EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

EXPERT REPORT OF DEBRA FROMER, M.D.

(Gynecare Prolift & Prolift +M General Report)

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin. My opinions set forth in this report are made to a reasonable degree of medical certainty, and are based on information and knowledge I have acquired from my education, training, personal experience in private practice, teaching, discussion and interaction with other pelvic surgeons in professional activities and conferences, research and review of medical literature and records.

BACKGROUND AND QUALIFICATIONS

I am the Chief of Female Pelvic Medicine and Reconstructive Surgery at Hackensack University Medical Center, the Program Director for the Fellowship in Female Pelvic Medicine and Reconstructive Surgery at Hackensack University Medical

Center, and Assistant Professor in Urology at Rutgers, the State University of New Jersey.

I received my Bachelor of Arts degree in Anthropology at the University of Pennsylvania, graduating Magna Cum Laude. Following my undergraduate education, I attended Tufts University School of Medicine and graduated with honors (Alpha Omega Alpha) in 1998. I completed my general surgical training in 1999 at Columbia Presbyterian Medical Center, where I stayed to complete my training in Urology in 2003. I subsequently joined the faculty practice at Hackensack University Medical Center where I have been practicing for the last 11 years. Over this time, I have cultivated a largely female urology practice, having been the only woman practicing adult urology in Northern New Jersey. Female patients make up approximately 90% of my practice. As such, my practice has largely become focused on female pelvic medicine and reconstructive surgery with high volumes of women seeking treatment for conditions such as urinary incontinence, prolapse, recurrent urinary tract infection, female sexual dysfunction, and pelvic pain. I am a frequently invited lecturer at medical and surgical conferences addressing urinary incontinence, the surgical management of prolapse and incontinence, and the treatment of overactive bladder. I am Board-certified in both Urology and in Female Pelvic Medicine and Reconstructive Surgery. I have performed over 1,000 anti-incontinence procedures, the vast majority of which consisted of polypropylene mesh slings.

In addition to my extensive experience with midurethral slings, I have performed over 500 surgical procedures for pelvic organ prolapse, the majority of which involve some form of polypropylene graft. My initial experiences post-residency involved a

combination of native tissue repairs, cadaveric dermal graft repairs and mesh augmented repairs utilizing Gynecare Gynemesh PS. My initial experiences revealed a higher recurrence that I would have liked with the native tissue repairs and with the cadaveric repairs. As such, my practice in pelvic organ prolapse repair shifted toward polypropylene mesh-augmented repairs. When Prolift became available, I gradually shifted to its utilization for patients who were good surgical candidates. I have utilized Anterior Prolift, Posterior Prolift and Total Prolift, and have performed over 150 cases utilizing Prolift of some kind. I have found that success rates were high, with a complication rate that was comparable to that of the other repairs that I had been doing, with the exception of vaginal exposure. My exposure rate gradually declined with surgical experience, as one would expect. In addition to vaginal repairs, I have also been involved with patients undergoing robotic sacrocolpopexy. In my current practice, I reserve this more invasive transabdominal technique for the rare patient who may require this as I have found it to be a more morbid means of achieving success than with a transvaginal repair. When Prolift was discontinued, I continued to utilize it until it was no longer available to me, as I consider it to be a great product from a safety and efficacy standpoint. In fact, there are many occasions to this day when I wish the product was still available for my use with appropriate candidates. At the current time, I am employing a combination of techniques for prolapse repair, including native tissue repairs, Uphold, and robotic sacral colpopexy.

As an Associate Professor at Rutgers New Jersey Medical School and as Fellowship Director for our Female Pelvic Medicine and Reconstructive Surgery program, I am actively involved in training urology residents from Rutgers New Jersey

Medical School and from New York Medical College as well as subspecialty training our fellows in Female Pelvic Medicine and Reconstructive Surgery. Many of these individuals go on to practice the techniques that I have taught them in order to deliver safe and effective use of the products.

In addition to training residents and fellows, I also have served as a preceptor for Ethicon in approximately 2012, and our institution has served as a physician training site for Ethicon. During this training, urology and/or gynecology residents, fellows and attendings were instructed on TVT, TVT-O and Prolift. This was accomplished with one to two hours of didactic training and two to four hours of hands-on cadaver training. My involvement in these training programs included preparation, planning and organization of the program, as well as contributing to both the didactic and the hands-on training as a proctor. The fees I have been paid by Ethicon in this regard have been under $5000.

My expert fees in this litigation are $600 per hour for review of medical literature, review of medical records and depositions, preparation of expert reports, and phone calls. For depositions, trial testimony, deposition preparation, and trial testimony preparation, I charge $8500 per full day and $4500 per half-day.

Accompanying this report is a copy of my current *curriculum vitae*, which includes a list of my publications, presentations, awards and other academic accomplishments.

MATERIALS I HAVE REVIEWED

In the course of preparing this report, I have reviewed numerous documents. I have examined the published literature on Gynecare Prolift Pelvic Floor Repair System ("Prolift") and Prolift +M, and more generally, the use of mesh to treat prolapse. I have

reviewed professional education materials produced by Ethicon, as well as the Prolift and Prolift +M Instructions for Use (IFU), patient brochures and professional education materials including the Prolift Surgeon's Resource Monograph. I have reviewed numerous company documents produced by Ethicon, including those specifically addressed in the deposition and video and live trial testimony of plaintiff experts Daniel Elliott and Anne Weber. I have also read the publicly available materials issued by medical societies and the Food and Drug Administration (FDA) regarding the use of transvaginal mesh to treat prolapse. A complete list of the materials that I have reviewed accompanies this Report, and will be supplemented as I review more materials.

THE DISEASE STATE OF PROLAPSE

Pelvic organ prolapse is defined as the descent of one or more pelvic organs. These organs include, the bladder (cystocele), the rectum (rectocele), the uterus (procidentia), the vaginal vault, or the bowel (enterocele). The compartments of the vagina are divided into the anterior compartment (the bladder and urethra), the posterior compartment (the rectum and the bowel), and the apex (uterus, vaginal vault or bowel). Approximately 70% of women with prolapse have 2 or all 3 compartments involved.[1]

The condition is seen on examination in 40-60% of women who have had children.[2] However, prevalence studies on the estimates of women with symptomatic pelvic organ prolapse estimate that 3% of women suffer from symptomatic pelvic organ

[1] Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL: Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol, 1997. 89:501–505.
[2] Maher C, et al: Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013:CD004014

prolapse, though this number may be an underestimate.[3] Using U.S. claims and encounters database from 2007 to 2011 in women age 18 to 89, Wu et. al. found that the lifetime risk of undergoing pelvic organ prolapse surgery was 12.6%.[4] Risk factors include pregnancy, childbirth, connective tissue abnormalities, denervation of the pelvic floor, aging, hysterectomy, menopause, and factors associated with chronically raised intra-abdominal pressure.[1] There is also evidence to suggest that some women carry a genetic predisposition to the development of pelvic organ prolapse.[5]

The symptoms of prolapse are often widely varied and include the sensation of having a vaginal bulge or protrusion as well as other undesirable symptoms of pelvic heaviness and a pulling sensation in the lower pelvis, back or vagina.[6] Patients often experience bladder, bowel and/or sexual dysfunction as a result of the condition.[7] Ghetti et al. found that sleep disturbance in women with pelvic organ prolapse is prevalent, occurring in half of the 407 women studied.[8] Furthermore, focus groups comprised of women with pelvic organ prolapse have clearly shown that feelings of shame regarding their condition, fear related to their symptoms, difficulties in talking to others about their condition and emotional stress from coping with the condition are prevalent.[9]

It is no surprise that pelvic organ prolapse can have a significant impact on a woman's sexual function. A qualitative study performed by Roos et al. showed that

[3] Nygaard et al, Prevalence of symptomatic pelvic floor disorders in US women. Vol 300, No. 11 pp 1311-1316, 2008
[4] Wu JM, et al: Lifetime risk of SUI or POP surgery. Obstetrics & Gynecology, Vol. 123, No. 6, 2014. 1201-1206.
[5] Allen-Brady K et al: Evidence for POP predisposition genes on chromosomes 10 and 17. Am J Obstet Gynecol, 2015, 212 (6):771.
[6] Jelovsek JE, et al: Pelvic organ prolapse. Lancet 2007. 369(9566): 1027-1038.
[7] Ellerkmann RM, et al: Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol. 2001. 185(6): 1332-1337.
[8] Ghetti C, et al: Sleep quality in women seeking care for pelvic organ prolapse. Maturitas. 2015. 80(2):155-61.
[9] Dunivan GC, et al: Pelvic organ prolapse: a disease of silence and shame. Female Pelvic Med Reconstr Surg. 2014 20 (6): 322-327.

women with pelvic organ prolapse had a negative image of their vagina, resulting in insecurity about their partner's sexual experience. Importantly, these fears, as well as discomfort from the condition and reduced genital sensations, resulted in decreased desire, arousal and difficulty achieving orgasm. As such, decreased motivation or willingness to engage in sexual activity, rather than drive, was the most common sexual dysfunction identified.[10]

The impact of these symptoms and issues on the quality of life in women with prolapse is clearly adverse. Very often in my own clinic I see active women of all ages refraining from exercise, social activity, and sexual intimacy as a direct result of their prolapse. This, in combination with the fear, shame, embarrassment, and often lack of knowledge about the condition and its treatments, can lead a woman to social isolation, difficulty in intimate relationships, and ultimately loss of dignity and the feeling that her womanhood is compromised.

Although pelvic organ prolapse can have a major negative impact on quality of life and overall sense of well-being, not all women with prolapse are symptomatic. While there is no obvious anatomic threshold correlating with the onset of symptoms, it is generally agreed upon that the hymenal ring is the landmark most correlated with bothersome symptoms in women with prolapse.[11]

The diagnosis of pelvic organ prolapse is most commonly made based on a patient's history and physical examination. The history often includes some combination of the symptomatology listed above, the sensation of an introital bulge, the feeling of

[10] Roos AM, et al: Pelvic floor dysfunction: women's sexual concerns unraveled. J Sex Med. 2014, 11(3): 743-52.
[11] Swift SE, et al: Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol. 2003, 114(3): 372-379.

pelvic "pulling," or the self-identification of a new vaginal mass. On physical examination, an abnormal bulge can be seen emanating from the anterior compartment, the apical compartment and/or the posterior compartment. Often times, more than one compartment shows deficits in support and evidence of prolapse. These deficits can be graded on a quantitative grading system, the most common being the pelvic organ prolapse quantitative pelvic exam (POP-Q) and the Baden-Walker halfway system.[12] Prolapse can also be visualized radiographically, with CT imaging, or MRI, though this modality is rarely necessary to make a diagnosis.

NON-SURGICAL TREATMENT OPTIONS FOR PROLAPSE

Pelvic organ prolapse is rarely a life-threatening condition, and therefore observation is considered an acceptable management option for asymptomatic or even mildly symptomatic patients. With this approach, patients can be observed for worsening prolapse or the onset of more bothersome symptom. However, some patients may progress to develop more severe prolapse and more bothersome symptoms necessitating intervention at some point.

Pelvic floor muscle training has been considered a potential option in the treatment and prevention of mild pelvic organ prolapse. Pelvic floor muscle exercises require time, motivation and proper technique in order to offer any benefit whatsoever. Wiegersma et al. compared the effects of pelvic floor muscle training and watchful waiting on women over the age of 55 with symptomatic and mild pelvic organ prolapse. Although pelvic floor muscle exercises resulted in a greater improvement in bother

[12] Persu C, et al: Pelvic Organ Prolapse Quantification System (POP-Q) – a new era in pelvic prolapse staging. J Med Life. 2011, 4(1): 75-81.

scores, this difference did not meet clinical significance. Nevertheless, 57% of women in the pelvic floor muscle training group reported improvements in overall symptoms compared with 13% in the observation group.[13] In a randomized controlled trial by Braekken et al., 19% of women in the intervention group showed improvement of one stage with the POP-Q grading system compared to 8% in the controls. This study also showed that pelvic organ muscle therapy prevented progression of prolapse in a subgroup of patients with slightly higher stage prolapse.[14]

The use of vaginal pessaries for the treatment of symptomatic pelvic organ prolapse dates back to the times of Hippocrates and represent the main alternative to surgical intervention for the treatment of prolapse. Pessaries are vaginal devices which provide mechanical support to the prolapsed organs, thereby relieving symptoms. Throughout the ages, techniques and objects used for reduction of prolapse such as leg binding, pomegranates, linen and cotton wool soaked in a variety of potions, cork, brass and rubber evolved into the non-reactive silicone that are currently used today.[15] Modern day pessaries come in a variety of shapes and sizes, designed to suit the individual patient's needs. They can be used in patients wishing to delay or avoid surgery. If a patient considers this form of therapy, she must be fitted for the appropriate device in the doctor's office, and some trial and error may be required before determining the optimal size and shape. Pessary maintenance includes removal, cleansing and replacement every 3 months, often in the physician's office, but sometime with the woman performing self-

[13] Wiegersma M, et al: Effect of pelvic floor muscle training compared with watchful waiting in older women with symptomatic mild pelvic organ prolapse: randomised controlled trial in primary care. BMJ. 2014, 22:349.
[14] Braekken et al: Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol. 2010, 203(2):170.
[15] Shah SM, et al: The history and evolution of pessaries for pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2006, 17(2):170-175.

care. The most common side effects are malodorous vaginal discharge, bleeding, erosions, ulcers, de novo incontinence and interference with sexual intercourse. Most minor complications occur in the setting of vaginal atrophy and can be treated or prevented with topical estrogen or pessary removal.

Tenfelde et al. looked at the symptom bother and quality of life in 56 women using pessaries for at least 12 months. Most of the women (55%) underwent pessary maintenance in the physician's clinic. Almost one-third of participants reported having complications such as vaginal erosion (where the pessary gets embedded in the vaginal tissues and causes ulcerative lesions), and 41% were considering surgical intervention in the future. Women considering surgery reported greater bother despite pessary use.[16]

Though vaginal pessaries are an excellent option for the patient wishing to avoid surgical intervention, younger, healthier and sexually active women are more likely to choose surgery rather than long-term pessary use.[17] It can be difficult if not impossible for women with pessaries to have intercourse due to the sheer volume of the pessary and difficulty with penetration. Furthermore, the maintenance required to sustain vaginal health and longevity of the pessary (removal, cleaning and replacement every 3 months) can be taxing for the older patient or simply not feasible for active, busy women. Pessary use is also limited by vaginal anatomy; women with vaginal length less that 7cm and/or introital width greater than 4 cm are less likely to be able to retain a pessary.[18]

[16] Tenfelde S, et al: Quality of life in women who use pessaries for longer than 12 months. Female Pelvic Med Reconstr Surg. 2015, 21(3):146-149.
[17] Clemons JL, et al: Patient characteristics that are associated with continued pessary use versus surgery after 1 year. Am J Obstet Gynecol. 2004, 191(1): 159-164.
[18] Clemons JL, et al: Risk factors associated with an unsuccessful pessary fitting trial in women with peliv organ prolapse. Am J Obstet Gynecol. 2004, 190(2):345-350.

SURGICAL TREATMENT OPTIONS FOR PROLAPSE: OVERVIEW

For women with symptomatic pelvic organ prolapse who have failed or declined more conservative management, surgical intervention may be indicated. The objective of surgical repair is to restore anatomy, quality of life and comfort, while at the same time minimizing morbidity and invasiveness.

A wide variety of surgical options exist in the management of symptomatic prolapse. These procedures are either reconstructive (restoring vaginal anatomy) or obliterative (closure of the vagina or colpocleisis). Though closure of the vagina is considered to be durable in terms of outcomes and many surgeons consider this a viable options for the management of prolapse, once it is done intercourse is not possible as the vagina is obliterated. As such, it should only be offered to women who are not sexually active and who do not wish to be sexually active in the future.

Reconstructive approaches vary depending upon the site of prolapse. Some procedures are isolated repairs of the anterior, posterior or apical compartments, while others may need to incorporate the repair of more than one compartment. Reconstructive surgical repairs can be offered using a number of approaches: vaginal, open abdominal, laparoscopic abdominal, and robotic abdominal. Vaginal approaches can be performed with or without the insertion of a graft, which can be composed of a biologic material or a synthetic material. Abdominal approaches most often utilize a synthetic graft for repair. In many cases, hysterectomy is performed at the time of reconstruction. Furthermore, stress urinary incontinence (leakage of urine with cough, sneeze or activity) often coexists with pelvic organ prolapse and its onset may even begin after surgical reconstruction (de novo). Therefore, surgical management of stress urinary incontinence

or de novo stress urinary incontinence needs to be considered at the time of reconstructive surgery.

TRANVAGINAL SURGICAL RECONSTRUCTIVE REPAIRS: NATIVE TISSUE REPAIR

Surgical repairs utilizing the patient's native in situ tissues have been in use for decades. The type of repair is dependent upon which compartment(s) are being surgically addressed.

Anterior Compartment

The anterior vaginal wall is the most common site of prolapse and more than 80% of all surgical repairs involve the anterior vaginal wall.[19] During an anterior colporrhaphy, the pubocervical fascia found deep to the vaginal mucosal surface and superficial to the bladder is imbricated together using absorbable sutures, thereby reducing the cystocele.

The anterior compartment is the most common site of recurrence with failure rates ranging from 30% to 60% after traditional native tissue repairs.[20,21] Variations in technique (repair of concomitant compartments, proper dissection, site-specific repair versus total repair) and differences in the definition of failure make comparisons between studies difficult.[22] Dietz et al. did a retrospective review of 166 patients after anterior colporrhaphy and found that 48% developed objective cystocele recurrence (POP-Q

[19] Olsen AL etal: Epidemiology of surgically managed managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol, 1997. 89:501-505.
[20] Brubaker L, et al: Surgery for pelvic organ prolapse. International Consultation on Incontinence (ICI), 2009. 4:1273-1320.
[21] Maher CF, et al: Surgical management of anterior wall prolapse: an evidence based literature review. Int Urogynecol J Pelvic Floor Dysfinct, 2006. 17:195-201.
[22] Van Geelen JM, et al: Where to for pelvic organ prolapse treatment after the FDA pronouncements? Int Urogynecol J, 2013. 24: 707-718.

Stage 2+), and 27% developed subjective recurrence with recurrent symptoms of prolapse. They found that the likelihood of recurrence was highest at 18 to 24 months post-operatively.[23] Griesen et al. looked at POP-Q measurements and quality of life questionnaires in 70 women with symptomatic anterior vaginal wall prolapse who underwent traditional native tissue repair of the anterior compartment with 5 years follow-up. They reported that 78% of women achieved symptomatic relief, 11% were re-operated, and 11% continued to experience symptoms of an introital bulge.[24] Fialkow et al. followed women for 10 years after primary prolapse repair. They found a recurrence rate of 25% with a cystocele being the most frequent element of primary (87%) and recurrent (72%) prolapse.[25] These outcomes are similar to data from other studies on traditional anterior colporrhaphy.[26,27]

It is important to note that anterior and apical compartment defects often coexist.[28] Addressing concomitant descent of the vaginal apex is critical when performing any kind of surgical reconstruction.

Apical Compartment

Apical prolapse is the result of weakened supportive fibromuscular tissue that connects the pelvic organs laterally to the pelvic walls. These tissues, the cardinal

[23] Dietz HP, et al: The natural history of cystocele recurrence. Int Urogynecol J 2014, 25(8):1053-1057.
[24] Griesen S et al: Subjective and objective results of anterior vaginal wall repair in an outpatient clinic: a 5-year follow-up. Int Urogynecol J, 2012. 23:883-886.
[25] Fialkow MF et al: Incidence of recurrent pelvic organ prolapse 10 years following primary surgical management: a retrospective cohort study. Int Urogynecol J 2008: 1483-1487.
[26] Lee U, et al: Native tissue repairs in anterior vaginal prolapse surgery: examining definitions of surgical success in the mesh era. Curr Opin Urol 2012. 22:265-270.
[27] Kapoor DS, et al: Reoperation rate for traditional anterior vaginal wall repair: analysis of 207 cases with median 4-year follow-up. Int Urogynecol J 2010, 21:27-31.
[28] Rooney K, et al: Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. Am J Obstet Gynecol. 2006, 195(6):1837-1840.

ligaments, the uterosacral ligaments, and the endopelvic fascia, along with the levator ani are responsible for the support of the uterus and the top of the vaginal vault. The most common surgical treatments of apical prolapse utilizing native tissues are plication of the uterosacral ligaments (uterosacral ligament suspension) and sacrospinous ligament fixation, whereby the apex of the vagina is suspended to the sacrospinous ligaments. Both procedures utilize delayed absorbable or non-absorbable sutures to fix the apex of the vagina to the pelvic ligaments.

Uterosacral ligament suspension is an intraperitoneal procedure that can be performed with a concomitant vaginal hysterectomy or in the patient who has had a prior hysterectomy. Though this procedure can be performed laparoscopically, data on that approach is lacking, and most often this procedure is performed transvaginally. Unfortunately, prolapse recurrence in patients undergoing this approach occurs in 25-30% of women, and potential complications include ureteral injury in 1-2%, and compression or entrapment of sacral nerve roots resulting in sciatic-type pain in up to 7% of patients. [29,30,31,32]

Sacrospinous ligament fixation can be performed after hysterectomy or while leaving the uterus in place (though most often the patient will undergo a concomitant hysterectomy) and can be performed without entry into the peritoneal cavity. It can either be performed bilaterally or unilaterally, though most surgeons opt for unilateral fixation. With unilateral fixation, the vagina is then deviated to the side where the suture

[29] Margulies RU, et al: Outcomes of transvaginal uterosacral ligament suspension: systematic review and metaanalysis. AM J Obstet Gynecol. 2010, 202(2): 124-134.
[30] Edenfield AL, et al: Vaginal prolapse recurrence after uterosacral ligament suspension in normal-weight compared with overweight and obese women. Obstet Gynecol. 2013, 121(3): 554-559.
[31] Flynn MK, et al: Sensory nerve injury after uterosacral ligament suspension. Am J Obstet Gynecol. 2006, 195(6): 1869-1872.
[32] Montoya TI et al: Sensory neuropathy following suspension of the vaginal apex to the proximal ureterosacral ligaments, Int Urogynecol J. 2012, 23(12): 1735-1740.

is placed. Potential complications include injury to the pudendal nerve bundle, which can result in hemorrhage and pudendal neuropathy. Recurrence rates after sacrospinous fixation are as high as 27%.[33]

Barber et al. published a randomized trial of 374 women undergoing sacrospinous ligament fixation versus uterosacral ligament suspension. At 2 years follow up, there was no significant difference in surgical success, defined by anatomic outcome (no apical descent greater than 1/3 into the vaginal canal or anterior/posterior vaginal wall beyond the hymen), symptom outcome (no vaginal bulge symptoms), and reoperation outcome (no re-treatment for prolapse). Surgical success rates were 59.2% after uterosacral ligament suspension and 60.5% after sacrospinous fixation. Serious adverse events occurred in 16% of patients in both groups. The rate of neuropathic pain requiring intervention was higher in the sacrospinous fixation group (12% vs. 7% in the uterosacral ligament suspension group.) Ureteral obstruction occurred in 6 patients (4%) in the uterosacral ligament suspension group.[34]

In 2018, JAMA published Jelovek's 5 year data on the OPTIMAL randomized clinical trial. This was an important study; as the authors put it: "Uterosacral ligament suspension (ULS) and sacrospinous ligament fixation (SSLF) are commonly performed pelvic organ prolapse procedures despite a lack of long-term efficacy data."[35] This study sought to provide long-term data on these traditional procedures, decades long in use, that up until now have not been studied in the long-term. The multicenter trial randomized

[33] Morgan DM, et al: Heterogeneity in anatomic outcome of sacrospinous ligament fixation for prolapse: a systematic review. Obstet Gynecol. 2007, 109(6):1424-1433.
[34] Barber MD, et al: Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. JAMA. 2014, 311(10): 1023-1034.
[35] Jelovsek JE et al: Effect of uterosacral ligament suspension vs. sacrospinous ligament fixation with or without perioperative behavioral therapy for pelvic organ vaginal prolapse on surgical outcomes and prolapse symptoms at 5 years in the OPTIMAL randomized clinical trial. JAMA, 2018.

374 patients with apical prolapse to pre-operative behavioral therapy and pelvic floor muscle training (BPMT) vs. usual pre-operative care, and then again to ULS versus SSLF. Surgical failure was defined as apical descent greater than 1/3 total vaginal length, or anterior or posterior vaginal wall beyond the hymen or retreatment for prolapse (anatomic failure), or bothersome bulge symptoms. Though the original OPTIMAL trial enrolled 374 patients, 285 patients enrolled in the follow up study and 244 completed the extended trial. At the end of 5 years, the surgical failure rate was 61.5% in the ULS group and 70.3% in the SSLF group, with anatomic failure in 45.6% in the BPMT group and 47% in the usual care group. Despite this high surgical failure rates, quality of life significantly improved. At the end of 5 years, 29% of patients in the ULS group and 20% of patients in the SSLF group developed granulation tissue, 26% in each group developed suture exposure, and 8.5%/4.5% required secondary prolapse surgery.

Posterior Compartment

Traditional posterior colporrhaphy involves imbricating the rectovaginal fascia with absorbable sutures thereby reducing the rectocele. Alternative native tissue repair strategies include site-specific repair and levator plication. Success rates typically range between 76%-96%. Complications can include sexual dysfunction, de novo dyspareunia (18%), and defecatory dysfunction.[36]

[36] Karram et al., Surgery for posterior vaginal wall prolapse, Int. Urogynecl J (2013) 24:1835-1841.

TRANSVAGINAL RECONSTRUCTIVE REPAIRS: GRAFT REPAIR

As a result of the high rates of failure of native tissue repairs, surgeons and device companies were incentivized to develop a more durable repair in order to give women more long-lasting pelvic organ support. The concept of a graft as an option for surgically reconstructing the vagina was a natural consequence to satisfy this unmet need.

Types of Grafts

There are currently four types of materials used in reconstructive pelvic floor surgeries: autografts, allograft, xenografts and synthetic mesh.

Autografts are harvested from the patient who is undergoing the reconstruction. The most common sites of graft harvest are fascia lata (thigh) and rectus fascia (lower abdomen. The use of these grafts is limited by the morbidity associated with graft harvesting in addition to the inconsistent quality and quantity of the graft.

Allografts are grafts processed from cadaveric human donors, and can be composed of cadaveric fascia or cadaveric dermis. Though utilization of these grafts eliminates the morbidity of harvesting allograft, allografts carry the potential risk of donor-related viral infection. Furthermore their outcomes are considered less beneficial when compared to autologous fascia and synthetic meshes, and a recent meta-analysis showed that biologic grafts offer no improvement over native tissue repairs.[37] [38]

Xenografts are composed of acellular extracts of collagen harvested from non-human sources (bovine, porcine). These materials pose a theoretical risk of infection, can

[37] Chen CC, Ridgeway B, Paraiso MF: Biologic grafts and synthetic meshes in pelvic reconstructive surgery. Clin Obstet Gynecol. 2007, 50(2):383-411.
[38] Maher C et al: Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev 2016.

be refused by patients due to religious/cultural barriers, and do not offer an improvement in outcomes over allografts and native tissue repair.

Synthetic meshes are available in both absorbable and non absorbable forms, with the most popular being non-absorbable due to its permanent nature. Though non absorbable mesh carries with it a potential risk of vaginal extrusion, its advantages include availability, sterility, permanence and consistency of quality, and lack of risk of donor to host disease transmission.

The ideal mesh should incur minimal inflammatory reaction, and should allow vascular and fibroblastic ingrowth. It should be macroporous (greater than 75 microns) and monofilament, to allow for this reaction.[39] Polypropylene mesh is one material that has these characteristics and is the more commonly employed mesh in pelvic floor reconstruction.

Graft repairs for Prolapse

The most recent and comprehensive meta-analysis on safety and efficacy comparing transvaginal mesh with native tissue repair was recently published in the Cochrane Review in February 2016.[40] This review included 37 randomized controlled trials (RCTs) involving 4,023 with quality of evidence ranging from very low to moderate. Of these 37 RCTs, 25 compared polypropylene mesh versus native tissue with 17 of these 25 involving anterior compartment repair, and 8 involving multi-compartment repair.

[39] Amid PK: Classification of biomaterials and their related complications in abdominal wall surgery. Hernia 1997:15-21.
[40] Maher C et al: Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev 2016.

With 1 to 3 year follow-up, women who had polypropylene mesh repairs were less likely to report awareness of prolapse than women who had native tissue repairs. From their data analysis, if "19% of women are aware of prolapse after native tissue repair, between 10% and 15% will be aware of prolapse after permanent mesh repair." Similarly, women who had transvaginal mesh repairs were less likely to have an objective recurrence on examination (stage 2 or greater). As one would expect, the rate of repeat surgery for prolapse was lower in the mesh group. When the authors limited the analysis to the anterior compartment, the benefit in the mesh group was more pronounced, and the quality of evidence was much improved due to reduction in heterogeneity. When the analysis was limited to multi-compartment repairs, the benefit in the mesh group was maintained.

Mesh exposure was reported in 12% of the women in the mesh group (10% after anterior mesh repairs and 17% after multi-compartment repairs), and 8% of women required surgery for mesh exposure. Injuries to the bladder were more common with mesh repairs, and only a single bowel injury was reported which did not affect the statistical outcome. Women in the transvaginal mesh group were more likely to report de novo stress urinary incontinence. This finding can be explained by the more successful anatomic outcome in the transvaginal mesh group. Prolapse recurrence or lack or restoration of normal vaginal anatomy after native tissue repair is less likely to unmask stress urinary incontinence than a more anatomic mesh-augmented repair. Nonetheless, there was no difference between groups in the rate of repeat surgery for stress urinary incontinence. There was no difference between groups with respect to de novo

overactivity, de novo dyspareunia, prolapse-specific sexual function questionnaire scores, and quality of life and satisfaction scores.

Grafts for Posterior Compartment Defects

In the patient with an isolated, primary posterior defect in the absence of an apical defect, the decision-making is relatively simple. Generally, neither biologic nor synthetic grafts offer improvement in subjective, objective or adversity outcomes relative to native tissue repair in this circumstance.[41] However, in the circumstance of recurrence in the posterior compartment after a failed repair, there is certainly a role for mesh-augmented repairs in the posterior compartment. Furthermore, in the circumstance where there is apical descensus in the absence of an anterior defect, a posterior mesh graft that can support the apex as well as the posterior compartment could be utilized.

Grafts for Anterior Compartment Defects

As previously stated, the anterior compartment has the highest risk of prolapse. As such, it would make sense to consider a graft in order to potentially reduce this risk of recurrence. In 1998, Nicita described what was then a novel technique of using a hammock-shaped polypropylene mesh in the anterior compartment.[42] In 2000, Migliari et al. published their data for a similarly fashioned polypropylene mesh for anterior compartment defects.[43] Both early studies showed low recurrence rates with minimal morbidity.

[41] Karram M et al: Surgery for posterior vaginal wall prolapse. Int Urogynecol J (2013): 1835-1841.
[42] Nicita J: A new operation for genitourinary prolapse. J Urol 1998: 741-5.
[43] Migliari R, et al: Tension-free vaginal mesh repair for anterior vaginal wall prolapse. Eur Urol 2000: 151-155.

In an extensive systematic review of 49 studies involving 4,569 women with anterior and/or posterior prolapse with a median follow up of 13 months, Jia et al. found that mesh reinforcement significantly reduced objective recurrence rates in the anterior compartment. They reported that the anatomic cure rate was 92% for non-absorbable mesh repairs, 77% for absorbable synthetic mesh, 82% for biological graft, and 71% for traditional native tissue repair.[44]

A 2013 systematic review by Maher et al. showed that synthetic mesh or biologic grafts for anterior compartment defect reduced the risk of recurrent cystocele over traditional native tissue anterior colporrhaphy, evident both on clinical examination and in the reduction of prolapse symptoms. When compared with absorbable mesh and porcine dermis augmented repairs, traditional anterior repairs had an increased risk of recurrent cystocele on examination, but no difference in subjective awareness of prolapse. When compared with polypropylene mesh, traditional anterior repairs had an increased risk of recurrent cystocele on examination, and an increased risk of awareness of prolapse. There were similar rates of reoperation for prolapse and no significant differences in quality of life between the two groups. Mesh repairs were associated with increased blood loss, longer operating room times, apical and posterior prolapse recurrences and de novo stress urinary incontinence. Mesh exposure in the vagina occurred in 11% of patients undergoing mesh-augmented repair.[45] These findings relative to mesh repairs vs. native tissue repairs are consisted with the more recent 2016 meta-analysis by Maher.

[44] Jia X, et al: Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systemative review and meta-analysis. BJOG. 2008, 115:1350-1361.
[45] Maher C, et al: Surgical management of pelvic organ prolapse in women. Cochrane database Syst Rev. 2013, 4:CD004014.

Surgical experience and technique likely play a significant role in occurrences of increased blood loss, apical and posterior prolapse recurrence, de novo stress urinary incontinence, and extrusion rates. Several studies indicate that surgeons who perform a higher volume of mesh-augmented repairs have fewer mesh-related complications.[22,46,47] Furthermore, if concomitant apical and posterior prolapse exists at the time of initial anterior repair, the decision to correct apical and posterior repair is largely subjective. For example, a patient with a high grade cystocele and low grade apical/posterior descensus may undergo an isolated cystocele repair augmented with mesh without addressing the other compartments, whereas another surgeon may correct the apical and posterior compartments. Such variations make interpretations of prolapse recurrence at sites other than the anterior compartment challenging. In addition, de novo stress incontinence can be avoided by the placement of a prophylactic midurethral sling. In my experience, most patients will consent to the addition of the midurethral sling in favor of maintaining continence.

Finally, we know that exposure rates can vary from surgeon to surgeon depending upon a number of factors, especially the depth of dissection when implanting transvaginal mesh. In my own retrospective analysis of patients undergoing transvaginal mesh repairs, we found an extrusion rate of 0%.[48] It is also my experience that when placing transvaginal mesh, it is important to maintain a full thickness dissection not only for the sake of reducing exposure rates, but also for the sake of reducing blood loss. Surgeons

[46] Achtari C, et al: Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910 (Vypro II) mesh. Int Urigynecol J Pelvic Floor Dysfunct. 2005, 16(5): 389-394.
[47] Vaiyapuri GR, et a: Use of Gynecare Prolift system in surgery for pelvic organ prolapse: 1-year outcome. Int Urogynecol J. 2011, 22(7): 869-877.
[48] Faber K, et. al: How I Do It: Techniques to avoid complications in transvaginal mesh surgery. Can J Urol. 2015, 22(3): 7844-7846.

operating through a split thickness, extensive dissection may report higher blood loss given the vascularity of the vaginal wall.

Balchangdra et al. reported on 159 consecutive women who underwent mesh augmented repairs by a single experienced surgeon. With meticulous dissection of a full-thickness vaginal epithelium, the authors reported a mesh exposure rate of 4%. The overall reoperation rate was 9% and the rate of intraoperative complications was 2% (including 1 patient with a bladder injury, and 2 patients with blood loss greater than 500cc and 1 patient requiring a transfusion). Only 1 patient (0.62%) required a transfusion. The rate of dyspareunia was 3%.

Grafts for Apical Compartment Defects

Feiner et al. published a systematic review of 30 studies including 2,653 women who had undergone one of several apical prolapse repair kits using mesh. Though success was defined variable, efficacy ranged from 87%-95% with follow up ranging from 26 to 78 weeks.[49] Another systematic review looked at complications and reoperation rates for native tissue apical repairs versus abdominal sacral colpopexy versus vaginal mesh kits and found that, though erosion rates for the mesh kits were higher at 5.8%, the rate of reoperation for prolapse recurrence was highest in the native tissue repair group (3.9%).[50]

Halaska et al. published a randomized controlled trial of 168 patients comparing sacrospinous fixation and Total Prolift for apical support defects in posthysterectomy

[49] Feiner B et al: Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review. BJOG 2009:15-24.
[50] Diwadkar GB et al: Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009: 367-73.

patients. At the end of 12 months, prolapse recurrence occurred in 39.4% of the sacrospinous fixation group and 16.9% of the mesh group. Though the exposure rate was high in this study (20.8%), there was no difference in quality of life improvements between the two groups.[51]

Mesh-Augmented Repairs for Recurrent Prolapse

The patient who fails a prior native tissue repair may be considered a good candidate for a mesh-augmented transvaginal repair with the goal of achieving better long-term results. Withagen M. et al. published a multicenter randomized controlled trial of 190 women with recurrent prolapse who undergoing either conventional vaginal repair versus a mesh-augmented repair. At a follow up of 12 months, anatomic failure (POP-Q stage 2+) was seen in 45% of patients undergoing traditional native tissue repair and in 10% of the patients undergoing mesh augmented repair. Six percent of the patients in the mesh group required excision of mesh exposures. Data from this study also reinforced the notion that addressing apical prolapse at the time of mesh-augmented repair is critical to the prevention of de novo prolapse in other compartments.[52]

ABDOMINAL SACROCOLPOPEXY

Given the high rates of recurrence with native tissue repairs for apical prolapse, abdominal sacrocolpopexy serves as potentially more durable option. With this

[51] Halaska M et al: A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol 2012: 301.
[52] Withagen M, et al: Trocar-guided mesh compared to conventional vaginal repair in recurrent prolapse: a randomized controlled trial. 2011, Obstet Gynecol 117:242-250.

procedure, a graft (polypropylene is most often employed) attaches the apex of the vagina to the anterior surface of the sacrum.

Estimates of prolapse recurrence vary from 0% to 22%, though this wide range could be accounted for by variation in graft selection (biologic vs. mesh). However, even with the usage of mesh, long-term studies have shown relatively high anatomic recurrence rates. Nygaard et al followed 215 patients for a median of 7 years after abdominal sacrocolpopexy and found an anatomic recurrence rate of 25%, with a mesh erosion rate of 10.5%. By the end of the seventh year, 16.7% of patients had additional surgery related to pelvic floor disorders.[53]

Despite this recurrence rate of 25% at 7-years follow up, abdominal sacral colpopexy has demonstrated more durability than native tissue repairs in multiple randomized trials.[38,54] This improvement should be balanced against the increased morbidity associated with this trans-abdominal, intra-peritoneal procedure. Longer hospital stays, longer recovery, increased cost and more serious complications associated with a transabdominal procedures may limit the selection of this technique.[38] Nygaard et al. performed a comprehensive review on outcomes of abdominal sacrocolpopexy. Intra-operative complications associated with this procedure include hemorrhage, cystotomy (up to 16%), enterotomy/proctotomy (up to 2.5%), and ureteral injury(up to 2%). Peri-operative and postoperative complications include mesh complications as well as more serious complications associated with transabdominal surgery with longer operative times, such as gastrointestinal complications and deep venous thrombosis or pulmonary

[53] Nygaard I, et al: Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. JAMA. 2013, 310(10): 1076.
[54] Siddiqui NY, et al: Mesh sacrocolpopexy compared with native tissue vaginal repair: a systematic review amd meta-analysis. Obstet Gynecol. 2015, 125(1):44-55.

embolus (up to 5%). Further, up to 15% of patients may require incisional hernia repair. More unusual, but serious complications reported included presacral hemorrhage, femoral nerve injury, obturator nerve injury, foot drop, fascial dehiscence, vertebral osteomyelitis, and gluteal necrotizing fasciitis.[55]

Whitehead et al. prospectively looked at gastrointestinal complications for 12 months following abdominal sacrocolpopexy in 322 women with advanced pelvic organ prolapse. "Nausea, emesis, bloating, or ileus" was identified in 18% of patients during their hospitalization and 10% at 6 weeks post-operatively. Ileus and small bowel obstruction was identified in 19 women (6%)—of those patients, 4 (1.2%) were re-operated on for small bowel obstruction, 11 (3.4%) were readmitted for medical management, and 4(1.2%) sustained a prolonged initial hospitalization.[56]

The rates of mesh erosion in sacrocolpopexy are not insignificant. In Nygaard's 7 year study, he found the mesh erosion rate to be 10.5%.[48] In a systematic review of 54 studies involving 7,054 women undergoing mesh surgery for apical prolapse, Jia et al found a mesh erosion rate of up to 21% in the sacrocolpopexy group.[57]

Given the morbidity and "maximal invasiveness" of open abdominal sacrocolpopexy, there has been a concerted effort in the last decade to minimize the risks of open sacrocolpopexy without compromising its efficacy. As such the move from open abdominal sacrocolpopexy to laparoscopic or robotic abdominal sacrocolpopexy has become the preferred approach for sacrocolpopexy in many major centers.[36] Though

[55] Nygaard IE, et al: Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004, 104(4): 805-823.
[56] Whitehead WE, et al: Gastrointestinal complications following abdominal sacrocolpopexy for advanced pelvic organ prolapse.Am J Obstet Gynecol. 2007, 197(1):78.e1-78.e7.
[57] Jia X, et al: Systematic review of the efficacy and safety of using mesh in surgery for uterine or vaginal vault prolapse. Int Urogyneol J. 2010, 21(11):1413-1431.

operating times are still longer than for transvaginal procedures, several studies looking at outcomes of minimally invasive abdominal sacrocolpopexy show shorter hospital stays and less blood loss relative to the open approach.[58,59] These improvements in morbidity must be balanced against longer operating times in the minimally invasive abdominal approaches.[46]

Unger et al. retrospectively reviewed 406 women who underwent either robotic-assisted laparoscopic sacrocolpopexy or conventional laparoscopic sacrocolpopexy. The re-operation rate for prolapse was 4.9% in the robotic group and 1.1% in the traditional laparoscopic group, the rate of blood loss greater than 500 cc was higher in the robotic group (2.5% vs. 0%), and the overall mesh erosion rate was 2.7%.[60]

TRANSVAGINAL MESH: GYNECARE PROLIFT PELVIC FLOOR REPAIR SYSTEM

Given the lack or durability with native tissue repairs and the morbidity, long operating times and costs associated with sacrocolpopexy, transvaginal procedures with mesh offered durability and less morbidity as a potential treatment of choice in the management of pelvic organ prolapse.

When I completed residency training, the "state-of-the art" procedure of choice in that institution at that time was using cadaveric tissues transvaginally, with bone anchor support, to reconstruct the anterior compartment. The vaginal apex was rarely addressed in cases where the primary defect was anteriorly. The outcome was a high re-operation

[58] Geller EJ, et al: Short-term outcomes of robotic sacrocolpopexy compared with abdominal sacrocolpopexy. Obstet Gynecol. 2008, 112(6):1201-1206.
[59] De Gouveia DSM, et al: Laparoscopic versus open sacocolpopexy for treatment of prolapse of the apical segment of the vagina: a systematic review and meta-analysis. 2014.
[60] Unger CA, et al: Perioperative adverse events after minimally invasive abdominal sacrocolpopexy. Am J Obstet Gynecol. 2014, 211(5): 547.

rate. And upon re-operation, the biologic graft placed in the months prior was usually found to be completely biodegraded. The alternative for a lower recurrence and re-operation rate at that time would have been open abdominal sacrocolpopexy, which was not a great option given the distinct increase in morbidity associated with an open transabdominal procedure.

In the early years of my practice as a young attending, mesh was being utilized more extensively in the treatment of stress urinary incontinence. As we began to see great safety and efficacy outcomes with polypropylene slings, we began to consider polypropylene as a means to augment our prolapse repairs. The first mesh graft that I used was Gynecare Gynemesh PS. Utilized in my hands almost exclusively for anterior compartment defects, I found the material to incorporate well into tissues and I found it highly effective in terms of prevention of recurrence, particularly in patients who had failed other procedures.

Over the course of five years, nine expert surgeons in France collaborated in an effort to develop a minimally invasive, transvaginal, durable and reproducible technique for prolapse repair. Their early retrospective study reported on 277 who had undergone repair with the product that would become Gynecare Prolift (which utilized Gynemesh PS) between January 2002 and December 2003. Intraoperative complications were low with rectal injury in 1 (0.36%), bladder injury in 3 (1.4%), hematoma/hemorrhage in 10 (3.6%) and intervention required in 2.8% with 90% of those interventions were associated with hysterectomy. The authors also noted that the intraoperative complications occurred during dissection as opposed to the mesh itself. The anatomic failure rate at 1 year was only 4%. Postoperative complications included symptomatic

tissue retraction in 1.8%, vaginal adhesion in 3.6% and vaginal mesh exposure in 9.2%. It was in these early studies that the innovators identified certain variables associated with exposure rates; they found that uterine conservation decreased exposure rate, that utilizing a longitudinal incision as opposed to a T incision or paracervical incision reduced exposure rates, and they found that exposure rates were higher in the anterior compartment that in the posterior compartment. By 2005, the TVM group had accumulated data on 687 patients.[61]

Utilizing the same technique, a prospective study involving 3 US sites and 9 EU sites enrolled 180 patients. Jacquetin et al. reported on 82 of the 90 women enrolled in the French arm of the study at the end of 5 years. Using a criterion of success (leading edge above the hymen and no bulge symptoms and no re-intervention), success was achieved by 90% of patients at 1 year, 88% at 3 years, and 84% at 5 years. Furthermore, quality of life improvements were sustained over the duration of the 5-year follow up period. Re-intervention for prolapse was required in only 5%, and mesh exposure was experienced in 16% with only 8 resections required. De novo dyspareunia was reported in 10%, but there were no new cases at the 5-year endpoint.[62]

The 5-year data of the US arm of the TVM study published by Miller et al. included 66 patients available at 5 year follow up.[63] Anatomic success (defined as POP-Q Stage 1 or less) was achieved in 88% at one year, 69% at 3 years, and 67% at 5 years. When success was defined as leading edge above the hymen, success rates were 89% at

[61] Caquant F et al: Safety of Trans vaginal mesh procedure: Retrospective study of 684 patients. J Obstet Gynaecol 2008: 449-456.
[62] Jacquetin B: Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogyncol J 2013.
[63] Miller D et al: prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse-5-year results. Female Pelvic Med Reconstr Surg 2011: 139-43.

the end of 5 years. Improvements in quality of life were sustained over the 5 years. The mesh exposure rate was 29%, with only 9 patients requiring partial mesh excision. The group reported on 3 patients with dyspareunia reported between 3 and 5 years, and 8 patients with resolution of preexisting dyspareunia.

When I was first exposed to Prolift, it was clear that this could be a game-changer for prolapse repair. It offered full coverage for any defect, anterior, apical or posterior, while minimizing the risks of a trans-abdominal procedure. And the published data supported its use.

Anterior Prolift was comprised of a body of monofilament, large pore, polypropylene mesh with four arms: 2 anterior arms designed to be passed through the obturator internus muscle just posterior to the inferior pubic rami bilaterally at the level of the bladder neck, and 2 posterior arms, each designed to be passed through the obturator internus muscle just distal to the ischial spines bilaterally. The arms of the mesh are passed through the lumens of 4 trocars passed through the medial thigh, exiting at the expected site under digital guidance. Though Anterior Prolift offered excellent support for isolated anterior defects, it was not ideal for support of high stage apical or posterior prolapse.

Total Prolift was designed to treat anterior, apical and possibly posterior defects. It was comprised of the same components as the Anterior Prolift, but the body of the mesh was larger and there were two additional arms—each designed to be passed through the sacrospinous ligament approximately 1 cm medial to the ischial spines bilaterally. The trocars for the posterior portion of the mesh were passed through 1 small incision on each buttock. The mesh could be completely wrapped around the apex of the vagina in a

post-hysterectomy patient, or the mesh could be divided at the apex and attached to the intact cervix for uterus sparing surgery. Posteriorly, the mesh could be extended distally as far as the introitus, or it could be trimmed at the apical portion of the posterior compartment depending upon the surgeon's preference to augment the repair posteriorly. Prolift served as "the best of both worlds" in that it was a transvaginal, minimally invasive procedure that could offer less morbidity compared to open or laparascopic sacrocolpopexy yet with significant improvements in durability over native tissue and biologic graft repairs.

The medical literature on Prolift shows that it provides significant benefit to well-selected patients, with a reasonable risk profile, particularly when used by surgeons who are experienced with the device, as these surgeons are most likely to implant the mesh as designed by the innovators who developed Prolift. De Landsheere et al. reported on a total of 524 consecutive patients who underwent Prolift repair between January 2005 and January 2009. With a median follow-up of 38 months, the re-operation rate for prolapse recurrence was only 3% and the rate of intervention for mesh-related complications was only 3.6%. Intra-operative complications were limited to 3 cystotomies (0.7%) performed during initial dissection and repaired, and 1 rectal injury (0.2%) performed during initial dissection and repaired. Three patients (0.6%) had post-operative blood loss greater than 400cc, all of whom required re-operation with either laparotomy or laparoscopy. Of the 19 patients (3.6%) who required intervention for mesh complications, 14 (2.7%) had mesh exposure requiring partial mesh excision. Mesh infection (0.2%), symptomatic mesh retraction (0.4%), rectal compression causing

constipation (0.4%) and symptomatic vaginal synechia (0.4%) were the rarer of the indications for interventions related to mesh complications.[64]

Altman et al. randomized 389 women with anterior prolapse to traditional anterior colporrhaphy or Anterior Prolift. The primary outcome was a composite of both objective and subjective criteria. At 1 year, 61% in the Prolift group achieved the primary outcome as opposed to 34% in the colporrhaphy group. Surgical correction of mesh-exposure occurred in 3.2% of patients in the Prolift group. Furthermore, for the Prolift group, the operative times were longer, the blood loss was higher, and the bladder perforation rate was higher.[65]

In addition to the RCTs discussed above, Prolift has demonstrated safety and effectiveness in a number of other RCTs comparing Prolift to some form of native tissue repair. Several RCTs demonstrate higher anatomic success with Prolift than with native tissue repairs, without sacrificing safety. Nguyen et al. randomized 75 patients with anterior vaginal prolapse to colporrhapy (38) versus Anterior Prolift (37).[66] Surgical success one year after surgery was achieved in 87% of the mesh group and in only 55% of the colporrhaphy group. De novo dyspareunia was reported in 16% of the colporrhaphy group and in 9% of the mesh group. The vaginal mesh extrusion rate was 5%. In Halaska's RCT, 168 patients with posthysterectomy vaginal vault prolapse were

[64] De Landsheere L, et al: Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obs and Gynecol. 2012, 206(83): e1-7.
[65] Altman D, et al: Anterior colpoprrhaphy versus transvaginal mesh for pelvic-organ prolapse. NEJM. 2011, 364(19): 1826-1836.
[66] Nguyen JN: Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008:891-8.

randomized to sacrospinous fixation (83) versus Total Prolift (85).[67] At the end of 12 months, prolapse recurrence occurred in 39.4% of the sacrospinous fixation group, and in 16.9% of the Total Prolift group. The symptomatic vaginal exposure rate was 5%, and most of these were treated without general anesthesia. Similar efficacy data was published by Svabik et al.: 70 patients with posthysterectomy vault prolapse were randomized to sacrospinous fixation with native tissue repair (34) versus Total Prolift (36). Anatomic success on clinical examination at the end of one year was achieved in 97% of the Prolift group and only 35% in the sacrospinous fixation group.[68] Similarly Silveira et al. published their RCT comparing native tissue repair (site specific repair with sacrospinous fixation) to Prolift in 184 patients.[69] At the end of one year, anatomic cure rates were significantly superior in the mesh group in the anterior compartment. Greater improvements in quality of life were achieved in the mesh group. There were no differences in sexual function between groups.

PROLIFT: POTENTIAL COMPLICATIONS

The complications of vaginal mesh in surgery for pelvic organ prolapse are not dissimilar from the complications that we see in all patients after any prolapse surgery. They can range from transient pain and small mesh exposures to more extensive exposures and dyspareunia. As per the AUA Position Statement on the Use of Vaginal Mesh for the Repair of Pelvic Organ Prolapse, “like with all surgeries, these

[67] Halaska M et al: A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J obstet Gynecol 2012: 301.
[68] Svabik K et al: Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014
[69] Silveira SRB et al: Multicenter, randomized trial comparing native vaginal tissue repair an synthetic esh repair for genital prolapse surgical treatment. Int Urogynecol J 2014.

complications may be due to surgical technique, the materials utilized, patient anatomy, or a combination of factors. It is also important to recognize that many of these complications are not unique to mesh surgeries and are known to occur with non-mesh POP procedures as well."[70] Some complications may be asymptomatic, requiring no further intervention. Others may require simple outpatient procedures to correct, and yet others may require more complicated procedures for correction.

Some centers have reported their experience with complications seen from mesh surgery. Blandon et al reported on 21 patients that they identified between 2003 and 2007 with complications after vaginal mesh surgery.[71] Of these 21 patients, only 9 patients were identified as having a mesh kit placed, and only 4 of these underwent surgery with Prolift. The remaining patients underwent surgery with non-Ethicon mesh kits (5), non-trocar based mesh augmentation (5), IVS tunneler (4) and "unspecified" (3). Further, many of these patients had undergone concomitant and subsequent procedures, including laparoscopic vaginal hysterectomy, cystotomy with repair, bone anchors, vaginal hysterectomy, Burch colposuspension, uterosacral ligament fixation, posterior repair, fascial grafts, and paravaginal defect repairs. One patient's initial repair was abdominal sacral colpopexy with mesh that subsequently needed to have abdominal exploration and excision of mesh. One patient even had Marlex mesh placed. With all of these multiple pelvic reconstructive surgeries that these patients have undergone, most of which not with Prolift, it is difficult to correlate the complications noted in this study with Prolift. Interestingly, the authors found that only 14% of patients were referred by their

[70] AUA Position Statement on the Use of Vaginal Mesh for the Repair of Pelvic Organ Prolapse. November 2011.
[71] Blandon et al: Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J, 2009

original surgeon. Though some believe this suggests a lack of awareness of complications by the original surgeon and an underestimation of complication rates, such a conclusion can not be proven from this data. Many patients may have self-referred themselves, or were referred by another physician while the original surgeon was still aware of the complications. Thus, the referral pattern is not an indicator of the original surgeon's awareness of complications. Another interesting point of this study is in the majority of these cases, the original surgeon was not subspecialized in female pelvic medicine. As the authors put it in their discussion, "This supports the notion that surgical technique may contribute to the development of these complications and emphasizes the need for specialized training." Finally, when it comes to describing the complications of Prolift, this limited retrospective study, with an N of 4, is not a good tool.

Abbott et al conducted a multicenter retrospective analysis of 347 patients seeking evaluation for mesh-related complications after SUI and/or POP surgery from 2006 to 2010 at 4 tertiary care centers.[72] Included in this study were women who had undergone sling surgery alone (50% of patients), transvaginal mesh or sacral colpopexy (26%), and sling surgery with concomitant transvaginal mesh or sacral colpopexy (24%). The most common complaints were mesh erosion (42.7%), pelvic pain (34.6%) and dyspareunia (30%). Of course, without a denominator, this study offers no information regarding the incidence of these complications in the setting of index surgery but rather show the breakdown of complaints in patients seen for complications after any kind of mesh surgery for prolapse or incontinence. The initial intervention for surgery was 49% and nonsurgical for 51%, with 59% of patients in the nonsurgical group eventually

[72] Abbott S et al: Evaluation and management of complications from synthetic mesh after pelvic floor reconstructive surgery: a multicenter study. 2014.

undergoing surgical intervention. Of note, 49% of women who sought management of a mesh-related complication underwent their initial procedure at a different facility. As above, this does not necessarily indicate lack of awareness on the part of the initial operating surgeon. As one might expect, the authors noted that patients in the sling only group had a more predictable and less complicated course than those treated with mesh for prolapse. Though this study indicates that patients seen in these referral centers with complications after transvaginal mesh had a more complicated course than those after slings or sacral colpopexy, the study did not break down TVM according to device, making it impossible to make conclusions regarding the course of these complications specifically after Prolift.

Contrary to the Abbott study, Tijdink performed a retrospective cohort study of 72 patients who underwent complete or partial mesh excision after sacral colpopexy (n=12), vaginal prolapse repair (n=48) and midurethral slings (n=15) that showed that excision of sacrocolpopexy mesh had a more morbid course than excision of vaginal mesh.[73] Patients in the SCP group required an abdominal approach for mesh excision, whereas patients in the transvaginal and sling group underwent transvaginal excision. A variety of mesh materials were excised in this study, including the IVS tunneler, Avaulta, Endofast Reliant, Gore-Tex, Mycomesh, Mersilene, Gynemesh, and Teflon, though Prolift was the most commonly excised mesh (40%). Pain was more commonly seen after transvaginal mesh procedures, whereas vaginal discharge and bleeding were more commonly seen after SCP. Intraoperative complications occurred in 4 patients: 3 patients developed bowel injuries including 1 bowel perforation during abdominal mesh excision

[73] Tijdink et al: Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh. Int Urogynecol J, 2011.

after sacral colpopexy, and 1 patient developed anuria as a result of iatrogenic, unnoticed ureteral obstruction during transvaginal mesh excision. Complications after excision were more common in the sacrocolpopexy group with intraoperative complications occurring in 23% (v. 1% p = 0.001). This finding is consistent with a study by South et al who found that abdominal excision of eroded mesh after abdominal sacrocolpopexy resulted in more serious complications compared to the vaginal route.[74] Tijdink et al also commented that when they analyzed the subset of patients who underwent Prolift at their center and they found that 0.6% required excision for severe mesh-related complications and 11% for minor complications. The authors also note, "Since it is impossible to generate a denominator for each mesh type and patients referred from other centers, no inference can be made on the overall incidence of mesh complications in the population or the relative complication rates related to individual mesh kits. Different types of mesh may be more likely to erode and others may be easier to excise." Nonetheless, the authors found that the vast majority of patients achieved symptom relief regardless of initial surgery.

Rac et al categorized complications using the Clavien-Dindo classification system in patients who underwent vaginal mesh excision surgery.[75] The authors retrospectively reviewed the records of 277 patients who had undergone vaginal mesh excision between 2007 and 2015 at their institution. Of these patients, 47.3% had at least 1 surgical complication, with a total of 155 complications. The most common complications were UTIs and vaginal yeast infections, accounting for 24% of the 155 complications. De

[74] South MM et al: Surgical excision of eroded mesh after prior abdominal sacrocolpopexy. Am J Obstet Gynecol, 2007.
[75] Rac G et al: Analysis of complications of pelvic mesh excision surgery using the Clavien-Dindo classification system. J Urol, 2017.

novo SUI accounted for 20% of the 155 complications, and de novo urge incontinence accounted for 7%. De novo POP accounted for 15.5%, and urinary retention due to bladder outlet obstruction accounted for 7.7%. Of the 155 complications, 49% were grade II (complications that require pharmacological treatment), 26% were grade I (any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention), 19% were grade IIIb (intervention requiring general anesthesia), 5% were grade IIIa (intervention not requiring general anesthesia), and 1.3% were grade IVa (single organ dysfunction, life threatening and requiring ICU management). Thus, minor complications (Grade 1 and 2) were the most common complications after mesh excision surgery accounting for almost 75% of all complications. Higher grade complications were most commonly related to de novo SUI requiring autologous fascial sling placement. Based on this study, catastrophic complications after mesh excision surgery are rare. Again, the authors did not break down the surgeries according to specific device.

However, studies that look specifically at complications in the absence of a denominator, particularly in small cohorts of patients and without comparisons to native tissue repairs, are less valuable than studies focused on larger populations with denominators, particularly when comparisons are made between treatment options. Dallas et al published a large-scale analysis of 110,329 women who underwent prolapse repair in the Journal of Urology. This study is the largest study to date exploring the risks and benefits of vaginal mesh for the treatment of prolapse. Data from the Office of Statewide Health Planning and Development were obtained from all women who underwent prolapse repair in California between 2005 and 2011. Logistic regression

models were used to identify which patient, surgical and facility factors were associated with the need for reoperation due to a mesh complication or recurrent prolapse. Of the 110,329 women who underwent prolapse surgery during this time period, 16.2% involved the use of mesh for prolapse repair. Though the overall reoperation rate was higher for those who underwent mesh repair (5.4% vs. 4.3%), multivariate analysis found that the mesh itself was not independently associated with repeat surgery. Rather, repair at a facility where there was a greater propensity to use mesh was independently associated with repeat surgery, supporting the judicious use of mesh in appropriately selected patients. In fact, their analysis suggests that certain proportions of mesh use for repairs resulted in optimal results. The authors noted in their discussion, "This provides evidence against the hypothesis that mesh itself or surgical volume alone is independently responsible for mesh based POP outcomes. Instead it provides evidence that patient selection has an important role." [76]

Dyspareunia and Pelvic/Genital Pain

Painful intercourse is commonly reported in both pre-menopausal and post-menopausal women, and especially in women with pelvic floor disorders. [7778] Deborah Coady states in her review of sexual pain that "one-third of women at some point in their lives experience painful sexual activity for 3 or more months."[79] Dennerstein et al. reviewed the effects of menopause on female sexual function and they found that by late

[76] Dallas KB et al: What impacts the all cause risk of reoperation after pelvic organ prolapse repair? A comparison of mesh and native tissue approaches in 110,329 women. J Urol 2018.
[77] Sobhgol SS et al: Rate and related factors of dyspareunia in reproductive age women: a cross sectional study. Int J Impot 2007:88-94.
[78] Dennerstein L et al: The menopause and sexual functioning: a review of the population-based studies. Ann Rev Sex Res 2003:64-82.
[79] Coady D: Chronic sexual pain: A layered guide to evaluation. Contemporary Ob Gyn. 2015.

menopause 88% of women experienced worsening dyspareunia.[55] When looking at urological patients, Elsamra et al. found that the prevalence of female sexual dysfunction was 63%.[80]

When evaluating dyspareunia as a complication with respect to Prolift, one must first consider the risks of dyspareunia associated with other common pelvic floor disorders and the surgeries that are used to treat them. Studies evaluating sexual function in women with prolapse have found baseline dyspareunia rates ranging from 8% to 43%.[81] [82] [83] [84] It has long been known that shortening of the vagina after prolapse repair due to the commonplace practice of trimming redundant vaginal tissue can result in dyspareunia. In 1961, Dr. Francis and Dr. Jeffcoate published "Dyspareunia following vaginal operations" in an effort to make light of this unfortunate and unnecessary outcome.[85] Similarly, Abdelmonem reported on a prospective observational study of 66 women who were scheduled to undergo abdominal (36) or transvaginal (30) hysterectomy for benign disease. Post-operatively, vaginal length and de novo dyspareunia were assessed. They found that vaginal length in the abdominal hysterectomy group was preserved and that only 5% developed de novo dyspareunia. However, in the transvaginal hysterectomy group, they found a significant reduction in vaginal length post-operatively, likely due to "trimming" of the vaginal wall for patients

[80] Elsamra S et al: Female sexual dysfunction in urological patients: findings from a major metropolitan area in the USA. BJU Int 2010:524-6.
[81] Weber AM et al: Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse. Am J Obstet Gynecol 2000:1610-5.
[82] Maher CF et al: Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol 2004:20-6.
[83] Handa VL et al: Sexual function before and after sacrocolpopexy for pelvic organ prolapse. Am J obstet Gynecol 2007:14-7.
[84] Barber MD et al: Sexual function in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol 2002: 281-9.
[85] Francis WJ, et al: Dyspareunia following vaginal operations. J Ob Gyn Brit Com 1961.

with prolapse, and a 20% de novo dyspareunia rate.[86] Holley et al. looked at 36 women who underwent sacrospinous fixation and found a de novo dyspareunia rate of 37.5%.[87] Silva et al. evaluated 110 women who had undergone uterosacral vault suspension for prolapse and they reported a dyspareunia rate of 26%.[88] Higgs. et al reported on a cohort study of 148 women who underwent abdominal sacral colpopexy and they found a de novo dyspareunia rate of 22%.[89] Handa et al[90] reported on sexual function before and 1 year after abdominal sacrocolpopexy in 224 women who had been recruited into the CARE trial (Colpopexy and Urinary Reduction Efforts trial) using sexual function questionaires. They found that 11 of the 76 patients who did not report pain limiting intercourse pre-operatively reported pain with intercourse 1 year after sacral colpopexy, for a de novo dyspareunia rate of 14.5% after colpopexy.

It is also well-known that posterior compartment surgery and perineorrhaphy can result in consequential rates of dyspareunia.[919293] Weber et al. evaluated 165 women who underwent surgery for prolapse and they found that dyspareunia occurred in 26% of women after posterior colporrhaphy and in 38% of women who underwent posterior colporrhaphy with Burch colposuspension.[94]

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[86] Abdelmonem AM: Vaginal length and incidence of dyspareunia after total abdominal hysterectomy versus vaginal hysterectomy. Euro J Ob Gyn and Reprod Biol 2010: 190-192.
[87] Holley RL et al: Sexual function after sacrospinous ligament fixation for vaginal vault prolapse. Obstet Gynecol 2002:281-9.
[88] Silva WA et al: Uterosacral ligament vault suspension, five-year outcomes. Obstet Gynecol 2006:255-63.
[89] Higgs P et al: Abdominal sacral colpopexy: an independent propspective long-term follow-up study. Aus New Zeal J Obstet GYnecol 2005: 430-4.
[90] Handa et al: Sexual function before and after sacrocolpopexy for pelvic organ prolapse. Am J Obstet Gynecol, 2007.
[91] Kahn MA et al: Posterior colpoprrhaphy: its effect on bowel and sexual function. Br J Ob Gyn 1997:82-86.
[92] Komesu YM et al: Posterior repair and sexual function. Am J Obstet Gynecol 2007: 101.
[93] Karram M: Surgery for posterior vaginal wall prolapse. Int Urogynecol J 2013: 1835-1841.
[94] Weber AM et al: Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse. Am J Obstet Gynecol 2000:1610-5

Understanding the risks of dyspareunia associated with all pelvic floor surgeries, one would not expect a dissimilar rate for mesh-augmented repairs, especially in those when a concomitant posterior colporrhaphy is performed. In fact, in Halaska's randomized control trial comparing sacrospinous suspension/native tissue repairs (n=83) to Total Prolift (n=85) there was no difference in rates of dyspareunia, pelvic pain or functional outcomes between the two groups.[95] Carey et al. reported on a randomized control trial comparing native tissue repairs versus mesh-augmented repairs. De novo dyspareunia was reported in 16.7% of the mesh group and 15.2% of the native tissue group.[96] Silveira et al. also reported no difference in sexual function scores in their randomized controlled trial of 184 women randomized to Prolift versus native tissue repair.[97] Withagen et al in their randomized controlled study of native tissue repair versus Prolift for the treatment of recurrent prolapse reported that 11.7% of patients in the native tissue group had lower abdominal/genital pain, while 10% of patients in the Prolift group had lower abdominal/genital pain. De novo dyspareunia was reported in 9% of the native tissue group and 10% of the mesh group.[98]

Furthermore, Abed et al. published a systematic review in 2011 of 110 studies that reported on graft erosion, wound granulation and dyspareunia after graft-augmented transvaginal repairs.[99] They found that the dyspareunia rate was 8.9% after synthetic

[95] Halaska M et al: A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatmet of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol 2012: 301.
[96] Carey M et al: Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. BJOG 2009: 1380.
[97] Silveira SR et al: Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int Urogynecol J 2014.
[98] Withagen MI et al: Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. ObGyn, 2011
[99] Abed H: Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J 2011.

graft repairs versus 9.6% after biologic graft repairs. The authors do cite inconsistencies across studies with regard to reporting on pre-operative dyspareunia and sexual activity as well as concomitant perineorrhaphy which could contribute to de novo dyspareunia.

Lowman et al. published their data on 129 women who underwent Prolift, the majority having undergone Total Prolift. The rate of de novo dyspareunia was 16.7%, with over 75% of patients with de novo dyspareunia describing the pain as mild or moderate. This rate of dyspareunia is well within or below the range seen with native tissue repairs, particularly posterior colporrhaphy where one can see rates of dyspareunia as high as 38%.[100] Despite the rate of 16.7% in patients after Total Prolift, 83% of patients with de novo dyspareunia stated that they would have the procedure done again.[101] Interestingly, of the 53 sexually active patients, 18 patients experienced dyspareunia prior to their surgery. Of those 18 patients, 15 were sexually active after their surgery, and 8 of those 15 no longer experienced dyspareunia after their surgery.

Altman et al. for the Nordic Transvaginal Mesh group reported on 105 sexually active women who underwent Prolift (46 anterior, 26 posterior and 33 total) and who were assessed 1 year post-operatively with the PISQ-12 questionnaire. It was found that sexual function scores worsened, but only in the behavioral-emotive and partner-related items of the questionnaire, which are unrelated to the surgery itself – reflecting the multifactorial nature of sexual function. Dyspareunia rates, however, was unchanged after surgery and improvements in physical function were observed.[102]

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[100] Weber AM et al: Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse. Am J Obstet Gynecol 2000:1610-5

[101] Lowman et al: Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008: 199, 707.

[102] Altman D et al: Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009: 127-33.

Dietz et al. published a meta-analysis to review dyspareunia rates after prolapse repair with or without mesh. They found Grade B evidence showing that the use of mesh in the anterior compartment was not associated with an increase in de novo dyspareunia when compared to traditional anterior repairs.[103]

In Jacquetin's five-year follow up on 90 women who underwent TVM (with a Gynemesh PS implant shaped nearly identically to the Prolift implant), the de novo dyspareunia rate was 10% in the 82 women available for follow up at the end of 5 years, with no new cases at the 5-year end point.[104] In another longer term study of 112 patients over 7 years, Kozal et al. reported a de novo dyspareunia rate of 16%.[105]

It is important to recognize that oftentimes surgeons perform perineorrhaphies or posterior repairs as well as vaginal hysterectomies concomitant with Prolift. In these circumstances, it can be difficult to determine whether or not the posterior repair or hysterectomy, known to have high rates of dyspareunia, is the source of sexual pain when evaluating the subjects of a particularly study. And, oftentimes perimenopausal or menopausal women are asked to abstain from intercourse for 4 to 8 weeks after vaginal reconstructive surgery. This abstinence in and of itself can result in dyspareunia.

Further, if we look closely at some studies assessing outcomes of Prolift and Prolift+M, we note that the authors attribute causes other than the mesh to de novo dyspareunia. For example, Milani et al published a prospective multicenter cohort study of 127 women with Grade 3 or worse prolapse who underwent implantation of Prolift +M mesh. At the end of 1 year, the rate of de novo dyspareunia was 2% (n=1). This one

[103] Dietz V and Maher C: Pelvic organ prolapse and sexual function. Int Urogynecol J 2013: 1853-1857.1
[104] Jacquetin B et al: Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013.
[105] Kozal S: et al: Morbidity and functional mid-term outcomes using Prolift pelvic floor repair systems. Can Urol Assoc J 2014.

patient with dyspareunia had pain on penetration that was attributed to vaginal dryness. At the end of 3 years, the rate of de novo dyspareunia was 9%, with the cause being attributed to vaginal atrophy, uterine prolapse and "unknown." [106] Ubertazzi et al published their 5-year outcomes after Prolift in women with Grade II prolapse or higher.[107] The authors performed a retrospective review of 76 patients after Prolift, of which 72 patients were available for the 5-year follow-up period. The rate of de novo dyspareunia was 13.3%. The authors note, "When using traditional repairs, de novo dyspareunia ranges from 14.5% to 36.1%. It is difficult to draw conclusions since the cause of dyspareunia is multifactorial and difficult to determine." The authors cited Jacquetin's article from 2013,[108] stating that it is difficult to assess "sexual activity beyond 3 years in studies of POP surgery as the outcomes are no longer reflective of the impact of the surgery, but only of the complexity of sexuality over time."

In summary, it is important to recognize that although Prolift does carry a risk of de novo dyspareunia ranging from 10% to 17% in the above sited studies, this is well within (if not below) the range of de novo dyspareunia rates that we see with sacral colpopexy and with the most common of native tissue repairs, where rates of de novo dyspareunia range can be as high at 38% in patients undergoing posterior repair (see above). Further supporting this is the 2016 Maher Cochrane Review that showed no

[106] Milani AL et al: Medium-term clinical outcomes following trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh. Int Urogynecol J 2012.
[107] Ubertazzi EP et al: Long-term outcomes of transvaginal mesh (TVM) in patients with pelvic organ prolapse: A 5-year follow-up. Euro J Ob Gyn Reprod Bio, 2018.
[108] Jacquetin B et al: Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J, 2013.

difference in de novo dyspareunia between polypropylene augmented repairs and native tissue repairs, regardless of compartments treated.[109]

Mesh Exposure/Erosion/Extrusion

As with the placement of all foreign bodies within the vagina, Prolift carries a risk of wound complications as a result of the mesh. Altman's randomized controlled trial of anterior colporrhaphy versus Prolift reported only a 3.2% rate of re-operation to correct mesh exposure. In a study of 75 patients who underwent Prolift, the exposure rate was 5.3% at a mean follow-up of 54 months.[110] In De Landsheere's study of 524 patients with 3 years' median follow-up after Prolift, only 3.6% of patients underwent re-operation for mesh exposure, and these only required partial mesh excision. In Jacquetin's 5-year study of 90 patients having undergone Total Prolift, 16% experienced mesh exposure and half of those required resection.

Elmer et al. looked at risk factors associated with mesh exposure in 353 patients who underwent Prolift. Mesh exposures, "of which the majority were mild-moderate," were reported in 8.6% of patients. Risk factors identified for mesh exposure were smoking, multiple childbirth, and somatic inflammatory disease.[111]

By contrast, Withagen et al. reported the results of their multicenter randomized controlled trial of 97 women undergoing conventional native tissue repair versus 93

[109] Maher C et al: Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev 2016.
[110] Benbouzid S et al: Pelvic organ prolapse transvaginal repair by the Prolift system: evaluation of efficacy and complications after a 4.5 years follow up. Int J Urol 2012: 1010-1016.
[111] Elmer C et al: Risk factors for mesh complications after trocar guided transvaginal mesh kit repair of anterior vaginal wall prolapse. Neurourol and Urodynam 2012: 1.

women undergoing Prolift for recurrent prolapse.[112] Their erosion rate was 17%. However, of the 14 patients who experienced mesh exposure, 9 were asymptomatic. In 5 patients, the exposures were excised with resolution, and the remaining 9 patients were treated with estrogen (2 of these exposures resolved and the remaining 7 were observed). Further, all patients had undergone prior surgery for prolapse and there were more patients in the Prolift group who had undergone prior sacral colpopexy. Such factors suggest that their higher rates of exposure may be related to the patient population that they were treating. As per the authors' discussion, "…the patient population only consisted of patients with recurrent pelvic organ prolapse, so more scar tissue of previous surgeries was present, which could have let to faulty or delayed healing with subsequent exposure." Interestingly, the exposure rate varied from center to center with a range of 0% to 100% and with a median of 0%. Further, this study included 22 gynecologic surgeons, with a range of surgical patients from 1 to 72. This extreme variability from center to center may reflect surgical experience and/or volume contributing to their outcomes, particularly with respect to the exposure rate. The authors themselves admit, "Another explanation for this fairly high rate of exposure could be the fact that in this multicenter trial of 13 participating centers, 22 surgeons, although all with an adequate level of experience, had their own learning curve."

Some may consider exposure and erosion to be complications unique to transvaginal mesh. The medical literature shows a wide range of mesh exposure rates that likely reflects the numerous variables that influence this complication, including vaginal integrity, surgical technique, and quality of mesh. However, any foreign body

[112] Withagen MI et al: Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. ObGyn, 2011

placed in the vagina for any type of repair can result in wound complications and this complication is not exclusive to transvaginal mesh. Luck et al. reported on suture erosion in patients undergoing posterior repairs. In this study, 99 patients underwent posterior repair with permanent sutures and 111 with absorbable sutures. Suture erosion/wound dehiscence occurred in 31% of the permanent suture group and in 9% of the absorbable suture group.[113] Toglia et al. looked at suture erosion rates in 92 patients who had undergone sacrospinous ligament suspension with non-absorbable suture with a mean follow up of 26.5 months. Suture related complications occurred in 36% of women with a mean time to presentation of 18.9 months.[114] Yazdany et al reported a 44.6% suture erosion rate in 88 patients undergoing uterosacral ligament suspension.[115]

Mesh Contraction/Retraction/Shrinkage

Shrinkage of tissue surrounding synthetic mesh after implantation for hernia repair has been reported by Amid et al as early as 1997.[116] Contraction has also been observed in animal studies.[117] However, the etiology and pathophysiology of this phenomenon is unknown.

Contraction or retraction associated with transvaginal mesh has been reported to occur in the medical literature and may or may not be symptomatic. Tunn et al made an attempt at objectifying mesh contraction by measuring the dimensions of the pre-

[113] Luck AM, et al: Suture erosion and wound dehiscence with permanent versus absorbable suture in reconstructive posterior vaginal surgery. Am J Obstet Gynecol 2005: 1626-9.
[114] Toglia MR et al: Suture erosion rates and long-term surgical outcomes in patients undergoing sacrospinous ligament suspension with braided polyester suture. Am J Obstet Gynecol 2008:600.
[115] Yazdany T et al: Suture complications in a teaching institution among patients undergoing uterosacral ligament suspension with permanent braided suture. Int Urogynecol J 2010: 813-818.
[116] Amid P: Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997:15-21.
[117] Garcia-Urena MA et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. Am J Surg 2007:538-42.

implanted mesh and comparing it to the measurement by introital ultrasound 6 weeks after implantation in 40 women after anterior or posterior mesh placement.[118] The majority of women underwent apogee or perigee by AMS (n=26), whereas the minority underwent Anterior or Posterior Prolift (n=14). The authors noted a significant reduction in mesh size as measured by ultrasound, suggesting that contraction occurs within the first 6 weeks. Ultrasound, however, is notoriously subjective and is not a good measure of objective sizing of mesh, which could have been placed in folded or curvilinear configurations. Further, technique can also play a role, confounding the ability to accurately measure mesh contraction. More importantly, the authors did not correlate this assumed contraction with any clinical symptoms. Hence, putting into question the clinical significance of mesh contraction.

In Caquant's retrospective review of 684 patients, retraction was observed in 11.7%. It was not explicitly stated how this was diagnosed or quantified. Nonetheless, only 2.8% of patients required reoperation for retraction.[119] De Landsheere reported only 2 of 524 (0.4%) patients requiring reoperation for "severe symptomatic mesh retraction."[120]

Despite these reports, some question whether or not contraction is significant or even if it exists. Dietz et al. analyzed mesh dimensions in women who had undergone anterior compartment trans vaginal polypropylene mesh repairs. Translabial ultrasound was performed twice on each of 40 women, once at the first post-operative appointment

[118] Tunn R et al: Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. US Obstet Gynecol, 2007.
[119] Caquant F et al: Safety of Trans vaginal mesh procedure: Retrospective study of 684 patients. J Obstet Gynaecol 2008: 449-456.
[120] De Landsheere L, et al: Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obs and Gynecol. 2012, 206(83): e1-7.

and once at the last postoperative appointment. The authors found no evidence in mesh shrinkage beyond 3 months after implantation.[121]

Some case reports review cases of "painful mesh contraction" without providing evidence that true contraction occurred or that, even if true contraction did occur, this contraction resulted in pain.[122] Even the authors of these reports admit that one of the explanations for these outcomes is "excessive tensioning of the arms or bunching of the mesh at implantation," a flaw in surgical technique that is explicitly advised against in most manufacturers' instruction and professional education. In fact, the Prolift IFU explicitly states that the surgeon should "avoid placing excessive tension on the mesh implant during placement." The Prolift Surgeon's Resource Monograph states that "tension-free placement is of great importance" and that "it is important to maintain the lack of tension at the site where the mesh wing enters the muscle," as "this local spot can be prone to postoperative pain if the wing junction wedges into the opening." Feiner et al. found in their case series of women with "symptomatic mesh contraction" the "contracted" portion of the mesh was at the lateral arms.

It would therefore make sense that over-tensioning of the arms of the Prolift, as warned against by Ethicon's Prolift IFU, Surgeon's Monograph and other Professional Education materials, should be avoided in order to reduce the risk of complications such as pelvic pain, dyspareunia, and distortion of the mesh thought by some to be 'symptomatic mesh contraction.'

[121] Dietz HP et al: Mesh contraction: myth or reality? Am J Obstet Gynecol 2011:173.
[122] Feiner B et al: Vaginal mesh contraction: Definition, clinical presentation, and management. Obstet Gynecol 2010: 325-30.

Inflammatory Response

Plaintiffs' experts have suggested that there may be an excessive inflammatory response with Prolift. This has not been the case in my experience, nor have I seen literature from peer-reviewed urology, urogynecology, or gynecology journals that have demonstrated this to be the case. The Performance section of the Prolift IFU describes to surgeons that the mesh elicits a "minimal to slight inflammatory reaction which is transient and followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into the surrounding tissue." This is an accurate description of the inflammatory process that takes place. On a histological level, there will be a chronic response, but based on my experience and my review of the medical literature, I have not seen a body of evidence showing that the chronic response has clinical implications for the patient.

Thomas et al., in response to unsubstantiated claims that mesh is implicated in the development of systemic conditions such as autoimmune diseases and carcinogenesis, performed a systematic review on the histologic inflammatory response to transvaginal polypropylene mesh.[123] The authors isolated 23 articles, including 625 human and 547 non-human subjects, for inclusion in the review. The authors concluded that after polypropylene mesh is implanted transvaginally, there is a local and immediate inflammatory response that decreases over time. Though none of the studies that the authors evaluated documented complete resolution of the inflammatory response, these studies were by limited follow-up (12-24 months). Thus, the authors concluded that there is no evidence in the medical literature to assess resolution of the inflammatory response.

[123] Thomas D et al: Histological inflammatory response to transvaginal polypropylene mesh: A systematic review. Urology, 2018

Nonetheless, there is no evidence in my experience or in the medical literature that this histological chronic response has an adverse clinical or systemic outcome.

Claims of Mesh Degradation and "Subclinical Infection"

There is no medical literature supporting the notion that polypropylene mesh "degrades" in any clinically significant way. Polypropylene by design is intended to be clinically present and supportive in its function. This is readily apparent to surgeons upon re-operation, if necessary. The mesh is found intact without clinical evidence of biodegradation. This is in comparison to biologic grafts, which on reoperation can often be invisible, degraded and non-supportive.[124] Given the large body of literature on the long-term efficacy of polypropylene slings with over 17 years of follow-up, it stands to reason that the polypropylene in slings, and in Prolift, does not degrade in any substantial or clinically significant way.[125]

Clave et al. examined explanted mesh implants from women with mesh erosion and/or "infection" after mesh-augmented reconstructions and compared them to a control group of pristine implants that had not been implanted. Using histological analysis, electron microscopy, and chemical analysis, electron microscopy, the authors concluded that oxidation of polypropylene "can neither be confirmed nor excluded" in the in vivo environment. Furthermore, the study compared mesh explanted from patients with complications to pristine, pre-implanted mesh, rather than mesh explanted from patients without complications. The authors therefore concluded that "prediction of normal in

[124] Woodruff AJ et al: Histological comparison of pubovaginal sling graft materials: a comparative study. Urology 2008: 85-89.
[125] Nilsson CG et al: Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013: 1265-9.

vivo sling material aging or the range of consequences in the clinical state beyond the observed samples is not possible. Due to small effective sample size, it is not possible to categorically conclude on the basis of statistical analysis even if a clear tendency is present." This study, therefore, by no means supports the notion that degradation, as seen under an electron microscope, has any clinical impact on the performance of polypropylene mesh in vivo.[126]

Similarly, there is no data in the medical literature supporting an in vivo, clinically significant "infection" related to polypropylene mesh. The tissue reaction that occurs after mesh placement is considered to be a normal physiologic reaction to a foreign body that occurs with all materials, including but not limited to sutures, grafts, surgical implants and metallic devices.

Wang et al. reported on a prospective "case-controlled study" comparing microbiological and immune-histochemical analyses of excised vaginal and peri-urethral tissue from 24 women with de novo urge symptoms after mid-urethral sling with TVT, Sparc or Monarc.[127] The authors performed urodynamics on each post-operative patient at the 6 month visit or when then complained of "urge sensation." "De novo urge symptoms" was defined as "any elevation of the detrusor pressure with urge sensation or urge incontinence during a filling cystometry, performed postoperatively." The authors enrolled 68 women as the "urgency" group. All patients were initially treated conservatively. Excision of the sling and peri-urethral tissue was performed for those patients whose symptoms persisted despite conservative measures. The control group

[126] Clave A et al: Polpropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010: 261-270.
[127] Wang AC et al: A microbiological and immunohistochemical analysis of periurethral and vaginal tissue in women with de novo urge symptoms after mid-urethral sling procedures—a prospective case-controlled study. Int Urogynecol J Pelvic Floor Dysfunct. 2008: 1145-50.

consisted of 12 women who had undergone midurethral sling but who developed symptomatic prolapse without de novo urgency symptoms 6 months after their sling surgery. These women underwent excision of peri-urethral tissue composed of vaginal wall, peri-urethral fascia and "possible urethral muscles" near the sling at the time of their prolapse surgery. The authors found higher levels of immune activity and gram-positive bacteria in the study group.

This study in no way provides evidence that any kind of "subclinical infection" or bacterial/immunogenic mechanism is responsible for de novo urgency after mid-urethral sling. Firstly, the sample size is exquisitely low, with only 12 "control" subjects. Furthermore, the control subjects are not truly controls, as their specimen did not include a portion of the sling and the tissues incorporated in the sling, whereas the study specimens did include those tissues and the sling itself. Additionally, the study is severely flawed by the fact that the patients routinely underwent UDS at 6 months post-operatively regardless of their symptomatic complaints, and they were considered to be surgical candidates for mesh excision by virtue of their urodynamics findings. Finally, de novo urgency is not a complication of sling surgery that is exclusive to midurethral slings. The rate of de novo urgency after mid-urethral slings is consistent with the rate of de novo urgency after non-mesh anti-incontinence procedures. If there was some mechanism exclusive to slings, such as this supposed "subclinical infection" causing de novo urgency, we would more globally see a significantly higher rate of de novo urgency in mesh slings versus other anti-incontinence procedures—and we do not. Similarly, the chronic inflammation seen on the slides of the asymptomatic controls debunks the theory that this physiological reaction results in adverse outcomes. For these reasons, this

study's conclusions linking de novo urgency after mesh slings to "subclinical infection" is invalid, and in no way suggests that the mesh used in Prolift causes this same "subclinical infection."

Longer Term Studies

Long-term data continues to be reported on Prolift and Gynemesh PS. In 2016, Santos et al. reported on a retrospective analysis of 54 women who underwent Prolift in Portugal between January 2009 and January 2016 with a mean follow up of 51.9 months. The anatomic failure rate (POPQ 2 or greater) was 5.6% while 89% of women remained asymptomatic of prolapse symptoms. Two patients developed exposure (3.7%), both managed successfully with excision. The de novo dyspareunia rate was 11%, though 11 patients had undergone concomitant perineoplasty. Their novo incontinence rate was 11% (urge 6.5%, stress 6.5%).[128]

Song et al published their experience with Prolift in 2016.[129] This retrospective review of 163 patients with mean follow up of 40 months reported POPQ Stage 0 in 56%, 69% and 66% and Stage 1 in 77%, 85% and 83% of patients in the anterior, apical and posterior compartments, and POP (respectively). Mean UDI and POPDI/PFDI were all significantly improved and the overall satisfaction rate was 85%. The vaginal erosion rate was 3.1%, de novo incontinence occurred in 13.5%, the rate of dyspareunia was 4.3%, 2.5% of patient developed pelvic pain.

[128] Santos et al: Transvaginal repair of genital prolapse with Prolift system: complications and outcomes after 6 years of use-a single-center study. (Abstracts) Euro J Ob Gyn Reprod Bio, 2016.
[129] Song W et al: Anatomical and functional outcomes of Prolift transvaginal mesh for treatment of pelvic organ prolapse. LUTS, 2016.

In 2016, Svabik et al reported their 6-year follow up data on the study described above, where 70 patients with post-hysterectomy vault prolapse and levator ani avulsion were randomized to Total Prolift (36) versus sacrospinous vaginal colpopexy with native tissue repair (34).[130] After 6.5 years (range 5-7.5 years), 33 patients in the Prolift group and 26 patients in the SSF group were available for follow up. During the follow up period, the re-operation rate for prolapse in the SSF group was 19%. The anatomic failure rate (prolapse at hymen or below) was 21% in the Prolift group and 77% in the SSF group ($p<0.001$). Using ultrasound criteria, the failure rate was 3% in the Prolift group and 58% in the SSF group ($p<0.001$). Though patients in the SSF group were less satisfied with their outcome than those in the Prolift group based on VAS ($p<0.001$), there were no statistical differences in PFDI, ICIQ-SF or PISQ 12 scores. The authors noted that the questionnaires "may be insufficiently sensitive to detect a difference of this magnitude." Three mesh exposures were identified before the 1-year follow up; while no new mesh exposures were diagnosed between 1 and 6 years of follow up.

Lo et al. reported on their retrospective review of 97 patients having undergone Prolift anterior and Total Prolift for total vaginal cuff eversion with a mean follow up of 52 months.[131] The objective cure rate (POPQ 1 or less) was 94% after Total Prolift Anterior and 80% after Anterior Prolift. The subjective cure rate (negative response to Q2 on POPDI-6) was 92% for Total Prolift with no significant difference in subjective cure rate between Total Prolift and Anterior Prolift. The overall incidence of pain, including groin pain, dyspareunia and pain during physical activity, was 3.1%. At the

[130] Svabik K et al: Randomized trial comparing vaginal mesh repair (Prolift Total) versus sacrospinous vaginal colpopexy (SSF) in the management of vaginal vault prolapse after hysterectomy for patients with levator ani avulsion injury – 6 years – follow- up. Int Urogynecol J, 2016.
[131] Lo TS et al: A 52-month follow-up on the transvaginal mesh surgery in vaginal cuff eversion. Tai J Ob Gyn, 2017.

end of 3 years, the rate of mesh exposure was 3.1%, with all 3 patients asymptomatic and not requiring surgical intervention.

Luo et al published their 8 year data on 154 women after Prolift and 21 women after Prosima.[132] Objective success (defined as the lowest point of prolapse never reaching the level of the hymen) was achieved in 99.4% and subjective success (defined as the patient reported absence of bulge symptoms and the absence of unacceptable symptoms, such as pain or incontinence) in 91.4%. 11% of patients reported chronic pain and discomfort at the perineum, operative incision or "puncture area." However, no patients abstained from sex due to postoperative discomfort. Vaginal mesh exposure occurred in 2 patients (1.3%) and bladder erosion occurred in one patient (0.64%).

Ubertazzi and his colleagues from Brazil published their 5-year outcomes after Prolift in women with Grade II prolapse or higher.[133] The authors performed a retrospective review of 76 patients after Prolift, of which 72 patients were available for the 5-year follow-up period. The cure rate (defined by leading edge less than or equal to 0 by POPQ, no bulge symptoms and no new treatment for prolapse) was 79%, with a re-operation rate for prolapse recurrence of 5.5% and for complications of 12.5%. The mesh exposure rate was 16.6%, though only half of these patients required re-intervention under general anesthesia. The authors noted in their discussion, "We recognize that the exposure rate of 16.6% found in our study may seem higher than those reported in the literature; however, this may be attributed to our learning curve. Nowadays we use small incisions, hydro-dissection for the proper separation of planes, re-absorbable

[132] Luo DY et al: Long term follow-up of transvaginal anatomic implant of mesh in pelvic organ prolapse. Scientific Reports, 2018.
[133] Ubertazzi EP et al: Long-term outcomes of transvaginal mesh (TVM) in patients with pelvic organ prolapse: A 5-year follow-up. Euro J Ob Gyn Reprod Bio, 2018.

monofilament sutures, and above all, a strict selection of cases." The rate of de novo dyspareunia was 13.3%. The authors note, "When using traditional repairs, de novo dyspareunia ranges from 14.5% to 36.1%. It is difficult to draw conclusions since the cause of dyspareunia is multifactorial and difficult to determine." The authors cited Jacquetin's article from 2013,[134] stating that it is difficult to assess "sexual activity beyond 3 years in studies of POP surgery as the outcomes are no longer reflective of the impact of the surgery, but only of the complexity of sexuality over time."

PROLIFT WARNINGS

The Prolift IFU clearly and adequately states indications, surgical technique, contraindication, warnings and precautions and adverse reactions associated with Prolift. The first warning, "users should be familiar with surgical procedures and techniques involving pelvic floor repair and nonabsorbable meshes before employing the GYNECARE PROLIFT Pelvic Floor Repair Systems" is of utmost importance. It is also warned in the IFU that "attention to patient anatomy…will minimize risks." So not only does the IFU recommend that surgeons understand pelvic floor surgical techniques associated with nonabsorbable mesh, but it also warns that surgeons should have familiarity with pelvic floor anatomy.

With regard to medical device warnings, it is first and foremost my opinion that all surgeons undertaking the complexity of the repair of pelvic organ prolapse should be familiar with pelvic floor anatomy, surgical techniques for traditional pelvic floor repairs, complications associated with those techniques, as well as the management of

[134] Jacquetin B et al: Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J, 2013.

complications before undertaking any form of mesh repair. The techniques utilized in the placement of Prolift are based on these techniques, and the complications associated with them are also similar to those experienced by women who undergo traditional repairs. Further, surgeons who perform mesh repair should also understand the basic concepts of utilizing mesh in a way that minimizes complications. Though the IFU, Surgeon's Monograph and professional education materials were all clearly adequate in laying out these surgical principles, warnings on adverse events and techniques for avoidance of these adverse events, it is my opinion that pelvic floor surgeons should already be aware of these facts, as they not only apply to Prolift, but also to all pelvic floor repairs.

In addition, it is clear from the literature cited above, from my own personal experience, and from common sense, that surgeons with experience in pelvic floor surgery, familiarity with pelvic anatomy, and those trained in proper technique and handling of mesh will have better outcomes after mesh-augmented repairs. The corollary to this is that surgeons without this experience, familiarity or training may have outcomes that fall below the standards for safety and efficacy. Ethicon has certainly done its part in warning users that they should be adequately trained before using the device.

As previously mentioned, the Prolift IFU warns that the surgeon should "avoid placing excessive tension on the mesh implant during handling." Given the tension-free design of the product, the fact remains that the surgical error of placing the mesh under tension may result in pain. Avoiding this surgical mistake is critical, as is made clear by the IFU, the Surgeon's Monograph and professional education materials.

The IFU also refers to a more detailed surgical technique description, which clearly and objectively lays out a standard, reproducible, and straightforward method. The IFU states, "correct use of the device will minimize risks."

The Prolift IFUs also appropriately reflect the potential risks that are reflected in the medical literature. Although earlier versions of the Prolift IFU do not make specific reference to pelvic pain and dyspareunia, these complications are known risks of any pelvic floor surgery. These risks are well known by the experienced pelvic floor surgeon, who is the intended user of Prolift. The Monograph also devotes entire sections of detailed discussion of the potential risks of hemorrhage, visceral injury, infection, erosion/exposure/extrusion, and dyspareunia and vaginal pain, including a review of the data that was available up until that point, and a detailed discussion on the management of these potential complications.

The Prolift professional education slide deck from 2007 also specifically addresses these complications, including reference to complications rates in the studies available at that time.

Despite the relevance of the Prolift IFU with respect to legal implications, the fact remains that not all implanting physicians read the IFU with any reliability. Kirkpatrick et al surveyed North American Urologists regarding the utilization of the IFU for mesh kit repairs for prolapse and found that 23% of implanting physicians had never read the IFU, and for those who have read the IFU, the most common frequency was once prior to first placement. This suggests that implanting physicians rely more heavily on other information sources such as intensive training, a robust body of medical literature, and medical conferences, rather than the IFU, in the planning, consent process and surgical

technique. The authors concluded, "The pertinent role the IFU plays in mesh related litigation belies our finding that many surgeons who utilize these kits infrequently, if ever, read them."[135]

Prolift +M

Ethicon developed Prolift +M in the hopes of improving patient comfort and reducing incidence of post-implant vaginal mesh exposure and de novo dyspareunia.[136] The hope was that a mesh that was partially absorbable would ultimately improve patient outcomes by leaving less permanent foreign body in the patient. To this end, Prolift +M was nearly identical to the original Prolift in surgical approach, with the exceptions that the mesh implant has an absorbable component, and that the posterior arms are curved differently. Specifically, the mesh implant of Prolift +M, also known as Gynecare Gynemesh M or Ultrapro, is knitted from approximately equal parts absorbable and nonabsorbable materials. The nonabsorbable component is identical to Prolene suture. The absorbable component is identical to Monocryl suture.[137] The pore size of Prolift +M's mesh implant is 2.5 mm upon implant and 3.5 mm following absorption of the Monocryl.[138]

Several studies have been published on Prolift +M demonstrating it to be an acceptably safe and effective option to treat prolapse. In 2011, Milani et al published a prospective multicenter cohort study of 127 women with Grade 3 or worse prolapse who underwent implantation of Prolift +M mesh. Follow-up was at 3 months and 1-year post-

[135] Kirkpatrick G et al: Transvaginal mesh placement and the instructions for use: A survey of North American Urologists. Urology Practice, 2018.

[136] ETH.MESH.039115790-792; ETH.MESH.00514901-921.

[137] Prolift +M IFU, ETH.MESH.01595616.

[138] Lensen EJM, et al: Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study. Int Urogynecol J 2013

operatively. Of the women undergoing implantation, 16.5% underwent concomitant hysterectomy, 28.3% underwent concomitant midurethral sling, 11% underwent concomitant perineal repair, and 4.7% underwent concomitant intervention for prolapse. Patients underwent anterior (32.3%), posterior (12.6%) or total (55.1%) Prolift +M depending on the site of prolapse. Anatomic success (prolapse stage 1 or less) in the treated compartment was 77.4%, and there were significant improvements in bother, quality of life, and sexual function at both time points compared to baseline. At the end of 1 year only 8.9% of women reported bulge symptoms. At 1-year follow-up, the mesh exposure rate was 10.2% (n=13). Of these patients, 7 underwent partial mesh excision with the remainder successfully treated with topical estrogen. At the end of 1 year, the rate of de novo dyspareunia was 2% (n=1). This one patient with dyspareunia had pain on penetration that was attributed to vaginal dryness. At the end of one year, 5 patients (3.9%) had new onset pelvic pain that was not present at 3 months. In 3 of these patients, pain was reported during daily life and in 2 of these patients pain was only experienced on palpation during examination and was considered to be the result of "vaginal wall stiffness." The authors believed that the low dyspareunia rate was encouraging with regard to the hypothesis that this partially absorbable mesh may have been an improvement over the original non-absorbable mesh. "This might be explained by the increased unidirectional elasticity and reduced fibrotic reaction, allowing adequate vaginal distension, which has been shown to be essential to allow normal sexual intercourse."[139]

[139] Milani AL et al: Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. Am J Obstet Gynecol 2011.

In 2012, the authors reported on the 3-year outcomes of these patients. In the longer-term study, 128 women with prolapse were included, and 109 (85%) provided 3-year follow up data. At the end of 3 years, anatomic success as defined above was 75.9% with significant improvements in quality of life measures, including pelvic symptoms and sexual function. Over the 3 years, the mesh exposure rate was 14.8% (n=19). Of these 19, 15 resolved with mesh excision and 4 had ongoing mesh exposures that were being treated conservatively. At the end of this follow-up period, no patients had de novo pelvic pain, but 3 patients (2.8%) had pain on palpation of the mesh during examination. The rate of de novo dyspareunia at the end of 3 years was 9%, with the cause being attributed to vaginal atrophy, uterine prolapse and "unknown." The authors concluded that the low incidence of pain and dyspareunia were encouraging.[140]

Bhatia et al. reported on their experience comparing sexual function outcomes of patients undergoing Prolift versus Prolift +M. This retrospective cohort study included 32 patients who underwent Prolift +M between 2008 and 2009 and compared their sexual function outcomes as measured by PISQ-12 to that of 39 patients who underwent Prolift between 2005 and 2009. At the end of 1 year, only 20 patients in the Prolift +M group and 20 patients in the Prolift group were still included in the study. At both the 4-month and 1-year follow up period, there was a significant improvement in total PISQ scores over baseline. When the outcomes of the Prolift +M were compared to that of Prolift, there was a significant improvement in postoperative sexual desire, comfort with

[140] Milani AL et al: Medium-term clinical outcomes following trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh. Int Urogynecol J 2012.

intercourse and overall sexual function at the end of 4 months.[141] However, this improvement lost statistical significance at the end of 1 year. Total PISQ scores also increased significantly in both groups at 4 months and at 1 year, and this improvement, though not statistically significant, was greater in the standard Prolift group than in the Prolift +M group.

In 2013, Dr. Khandwala published his one-year outcomes in 157 patients who underwent Prolift +M for prolapse between 2009 and 2010 with a mean follow-up of 13 months.[142] Success was defined by a composite score that included POP-Q lower than stage II; and PFDI Q#3: "Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?" must be answered no, or if yes answered not at all bothersome; and patient satisfaction as determined by the Subject Global Impression question: "Compared to how you were doing before the recent pelvic floor operation, would you say that you are: much better, a little better, about the same, a little worse or much worse" must be answered "much better" or "a little better." It order to achieve success by this composite, each of these criteria must have been met. Adverse events that were assessed included bothersome de novo incontinence defined as new onset incontinence requiring intervention, mesh retraction as determined by vaginal examination (ant mesh retraction or banding, point tenderness or generalized tenderness was assessed and noted," dyspareunia, mesh exposure, blood loss and postoperative complications.

[141] Bhatia N et al: A comparison of sexual function outcomes 1 year after undergoing a transvaginal mesh procedure using polypropylene mesh vs. hybrid polypropylene/poliglecaprone mesh. Female Pelvic Med & Recon Surgery 2012.

[142] Khandwala S: Transvaginal mesh surgery for pelvic organ prolapse: one-year outcome analysis. Female Pelvic Med Reconstr Surg 2013.

Of the 157 patients who underwent surgery, 134 (85.4%) were followed to the 12-month visit. The composite success core was 88.1%, and there was a significant improvement in all parameters and subscores of the PFDI compared to baseline. The exposure rate was 2.2% (3/134), one which required excision in the operating room and 2 who were managed conservatively. The de novo dyspareunia rate was 6% (3/50), two of whom improved after a "perineal relaxation procedure" as the dyspareunia was thought to be due to an overaggressive perineoplasty, and the other was treated successfully with topical estrogen. The rate of de novo urge incontinence was 11.2% (n=15) and none required pharmacologic or surgical intervention. Recurrent UTI occurred in 2.2% (n=3) and none had mesh erosions into the bladder. The authors noted that their dyspareunia rate of 6% fares well in the "typically quoted dyspareunia rate for mesh prolapse surgeries…between 14.5% and 36.1%," citing Handa et al which studied sexual function after sacrocolpopexy and Lowman et al which specifically looked at rates of dyspareunia.[143] [144] They postulated, "This low incidence could be due to the properties of the PP-PG system and the warp knitting that allows increased unidirectional elasticity and reduced fibrotic reaction that may benefit vaginal distention during intercourse," and cited the first Milani article above. Similarly, the authors noted that their rate of mesh exposure (2.2%) was lower than "the 8 to 15% quoted in the medical literature," citing Dwyer et al and Achtari et al, both studies of Atrium mesh dated 2004 and 2005 respectively.[145] [146] Nonetheless, the authors do note that longer follow up is essential.

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[143] Handa VL et al: Sexual function before and after sacrocolpopexy for pelvic organ prolapse. Am J Obstet Gynecol. 2007

[144] Lowman JK et al: Does the Prolift system cause dyspareunia? Am J Obstet Gynecol, 2008.

[145] Dwyer PL et al: Transvaginal repair of anterior and posterior compartment prolapse with Atrium polypropylene mesh. BJOG 2004.

In 2013, Lensen et al published a retrospective study of prospectively collected data comparing outcomes of Prolift versus Prolift +M in patients deemed to be at high risk for prolapse recurrence. This was defined as either recurrent POP stage II or higher and/or primary POP stage III or higher. Failure was defined as a composite outcome: POP beyond the hymen and vaginal bulge symptoms or surgical POP reintervention within 12 months. Other outcomes included anatomic failure, subjective improvement, mesh exposure rate, changed in bother and quality of life measure by the UDI, complications, re-operation rates, urinary incontinence, dyspareunia and pain. In the study period between 2005 and 2011, 641 patients met the inclusion criteria and 12-month follow up data was available for 569 patients, 347 in the Prolift group (2005-2009) and 222 in the Prolift +M group (2009 and beyond). Data was collected prospectively and on consecutive patients. Patients in the Prolift group underwent significantly more concomitant posterior and anterior colporrhaphies, and had a significantly higher rate of having undergone prior prolapse repairs. In addition, operating time and blood loss were significantly higher in the Prolift group. At the end of 12 months, the composite failure rate was 8% in the Prolift +M group and 4% in the Prolift group (not statistically significant). However there were more failures in the untreated compartments in the Prolift group. Although high, there was no difference in de novo dyspareunia rates between the two groups. The exposure rate at the end of 12 months in the Prolift group was 12% as opposed to 5% in the Prolift +M group. Of those with exposures, 39% in the Prolift group were treated surgically versus 42% in the Prolift +M group. Although the authors partially attribute this difference in exposure rate to the composition and

[146] Achtari C et al: Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910 (Vypro II) mesh. Int Urogyncol J Pelvic Floor Dysfunct 2005.

construction of the partially absorbable mesh, they do acknowledge "the increased experience could play a role in decreasing the exposure rate, since clinical and surgical experience has previously been shown to be inversely associated with the risk of exposure." In addition to this, the patients in the Prolift group had undergone a higher number of prior prolapse repairs, and had longer operating room times and higher rates of blood loss (the latter two factors were likely indicative of early surgeon experience). These factors likely influenced the higher exposure rates noted by the authors in the Prolift group.

Nonetheless, patients in the Prolift +M group required more re-interventions for exposure. The authors concluded, "owing to the study design it was impossible to know whether [this difference in exposure rates] was mainly due to the mesh properties or the increasing experience of the surgeons or a combination of both. Other complications and patients' overall improvements were similar."[147]

Khandwala et al published a retrospective case series of 77 women between 2008 and 2011 who underwent vaginal mesh hysteropexy with Prolift +M for advanced uterovaginal prolapse. Success was defined as POP-Q stage less than II and patient satisfaction as per PFDI-20 question #3. Other outcomes included complications such as mesh exposure, mesh retraction, dyspareunia, urinary incontinence and voiding dysfunction. Mean follow-up was 13.7 months. Most patients (96.1% underwent Total Prolift +M. The failure rate as defined above was 14.3%. The subjective failure rate was 7.8%. The mesh exposure rate was 6.5%, with only 1 patient requiring revision. The rate of recurrent UTI was 2.6% and the rate of de novo stress incontinence was 3.9%. The

[147] Lensen EJM, et al: Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study. Int Urogynecol J 2013.

rate of de novo dyspareunia was 3.7%. The authors suggested that this low dyspareunia rate could be the result of leaving the uterus in situ, noting that deep dyspareunia "may result from scarring and tethering at the vaginal vault following hysterectomy." [148]

In 2014, a Taiwanese group reported on their non-randomized controlled comparative study of 72 women undergoing laparoscopic sacrocolpopexy (LSC) versus Total Prolift +M (TVM). Patients were included if they had symptomatic POP Stage 2 or greater and were excluded if they had a previous mesh repair or hysterectomy within 6 months of surgery. Concomitant surgeries were performed "as indicated." Follow up was at 3, 6 and 12 months and then annually thereafter. Success was defined as the absence of vaginal bulge sensation and POPQ Stage 1 or less. Of the 72 patients enrolled, 3 (1 LSC, 2 TVM) were lost to follow up, leaving 39 women who underwent LSC and 30 who underwent TVM. At baseline, the patients in the LSC group were significantly younger, had lower BMIs, and had a lower percentage of patients post-menopause. The number of concomitant surgeries was comparable between the groups. Post-operatively, there were no significant differences between the groups with respect to efficacy and stress incontinence. At the end of one year, the dominant anatomic recurrence after LSC was in the anterior compartment whereas that after TVM was in the apical compartment. One patient in the TVM group (3.3%) had vaginal mesh exposure that was managed by mesh excision. The rates of dyspareunia were unchanged before and after both procedure and were not significantly different between the two groups. [149]

[148] Khandwala S et al: Role of vaginal mesh hysteropexy for the management of advanced uterovaginal prolapse. J Reprod Med 2014.
[149] Liu C, et al: A comparative study of laparoscopic sacrocolpopexy and total vaginal mesh procedure using lightweight polypropylene meshes for prolapse repair. Taiwan J Obstet Gynecol, 2014.

Quemener et al published their retrospective experience specific to re-intervention of 250 patients who underwent Prolift +M between 2009 and 2011 at a single center. Each patient received a phone call to determine if any re-intervention had been performed at an outside center with a median follow-up of 20 months. The data were then compared to previously collected data on 524 patients who had undergone Prolift between 2005 and 2009 by the same surgeons at the same center. A total of 269 patients were recruited, but 13 were lost to follow up; 3 refused participation in the study, 2 died of unrelated causes, and 1 had bladder extrophy. Of the remaining 250 patients, the re-intervention rate was 8% (n=20). Re-intervention was due to post-surgical hemorrhage in 3 patients (1.2%), mesh exposure in 5 patients (2%) treated with partial mesh excision, recurrent prolapse in both treated and untreated compartments in 3 patients (1.2%), and stress incontinence in 12 patients (4.8%). Re-intervention for mesh exposure usually occurred between 4.7 and 7.5 months. When compared to the results of their prior study of 524 patients who had undergone Prolift, baseline demographics were similar except that the patients in the Prolift +M group were significantly older, and the patients in the Prolift +M group had fewer concomitant hysterectomies. They found no significant difference in re-intervention rates for exposure, stress incontinence or prolapse recurrence. The authors commented on their low rates of exposure with respect to both meshes and stated that their surgeon's seniority and technical experience may have played a role. They also postulated that the rates of exposure in both groups may have been too low to detect a difference between them. They also commented that they did not detect a difference between the two meshes with respect to mesh infection, mesh retraction, rectal compression and symptomatic synechia. The authors states, "There do not seem to be

any advantages in terms of rates of rates of reintervention using partially absorbable mesh." With regard to dyspareunia, though they note that the data from Milani et al is encouraging, "The rate of reintervention for de novo dyspareunia is very low in the literature, and only a prospective comparative study between partially- and non-absorbable meshes could show any benefit on this specific item."[150]

Van de geest et al (2015) reported their interim data on a prospective randomized multicenter study comparing outcomes after Prolift +M versus that of native tissue repair in 163 women with primary POP between 2011 and 2013. At the end of 12 months, the mesh exposure rate was 4%, and there were no detectable differences in outcomes. De novo dyspareunia (3.1% vs. 9.4%) and de novo pain (3.1% vs. 1.6%) were "equally distributed within groups."[151]

Below is a summary of the studies listed above:

	Follow up	Exposure	De Novo Dyspareunia	De novo Pelvic Pain
Milani et al, 2011 (n=127)	12 Months	10.3%	2%	3.9%
Milani et al, 2012 (n=128)	36 Years	14.8%	9%	0%
Khandwala 2013 (n=157)	13 Months	2.2%	6%	
Lensen et al, 2013 -Prolift +M (n=222) -Prolift (n-347)	12 Months	 5% 12%	 20% 19%	 14% 8%
Khandwala et al 2014 (n=77)	13.7 Months	6.5%	3.7%	

[150] Quemener J et al: Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months medican follow-up outcomes. Eur J Ob Gyn Reprod Bio 2014.

[151] Van rumpt-van de geest DA et al: Vaginal repair of primary pelvic organ prolapse: trocar guided partially absorbable mesh or native tissue: A randomized controlled trial. Int Urogynecol J 2015.

Liu et al, 2014 (n=30)	12 Months	3.3%		
Quemener et al, 2014 (n=250)	20 Months	Re-intervention 2%		
Ven de geest et al, 2015 -Prolift +M -Native Tissue Repair	12 Months	4%	3.1% 9.4%	3.1% 1.6%

In conclusion, the cumulative results of all of these studies indicate that utilizing a partially absorbable mesh does not eliminate the risks of prolapse surgery, including the risk of mesh exposure, dyspareunia and chronic pelvic pain. Further, the evidence does not conclusively support the hypothesis that a partially absorbable mesh can even mitigate these risks or reduce the rate of re-intervention, as many of these studies show the rates of exposure, dyspareunia, pain and re-intervention to be within the range of reported outcomes after prolapse repairs with non-absorbable mesh, and for even native tissue repair (with the exception of mesh exposure). Thus, despite the theoretical benefits of a partially absorbable over a non-absorbable mesh for the surgical management of POP, the evidence to date does not prove the hypothesis that such theoretical benefit translates into clinical advantages with reduction in rates of exposure, pain, dyspareunia and re-intervention. As such, while Prolift +M was an appropriate treatment option for prolapse with an acceptable safety profile, it did not eliminate or mitigate the potential for recurrence, dyspareunia, mesh exposure, pelvic pain or other potential risks of prolapse repair.

PROLIFT +M WARNINGS

The Prolift+M IFU clearly and adequately states indications, surgical technique, contraindications, warnings and precautions and adverse reactions associated with Prolift+M. The first line of the IFU, after "Please read all information carefully," states: "Failure to properly follow instructions may result in improper functioning of the devices and lead to injury," indicating that surgeons must take care to follow appropriate technique, both basic surgical technique with respect to pelvic floor reconstruction and specific technique with respect to Prolift+M. The importance of surgical technique and surgeon familiarity with anatomy is repeated on multiple occasions throughout the IFU. Under WARNINGS, the IFU clearly states, "Use the GYNECARE PROLIFT+M Systems with care, and with attention to patient anatomy and to proper dissection technique, to avoid damage to vessels, nerves, bladder, bowel, and vaginal wall perforation. Correct use of the GYNECARE PROLIFT+M Systems components will minimize risks." Under PRECAUTIONS the IFU further states, "Users should be familiar with surgical procedures and techniques involving pelvic floor repair and synthetic meshes before employing the GYNECARE PROLIFT +M Systems."

As I have stated earlier in this report with regard to the PROLIFT IFU, it is my opinion, and certainly basic common sense, that all surgeons undertaking the complexity of the repair of pelvic organ prolapse should be familiar with pelvic floor anatomy, surgical techniques for traditional pelvic floor repairs, complications associated with those techniques, as well as the management of complications before undertaking any form of mesh repair. The techniques utilized in the placement of Prolift+M are based on these techniques, and the complications associated with them are also similar to those

experienced by women who undergo traditional repairs. Further, surgeons who perform mesh repair should also understand the basic concepts of utilizing mesh in a way that minimizes complications. Though the PROLIFT+M IFU, Prolift Surgeon's Monograph and professional education materials were all clearly adequate in laying out these surgical principles, warnings on adverse events and techniques for avoidance of these adverse events, it is my opinion that pelvic floor surgeons should already be aware of these facts, as they not only apply to Prolift+M, but also to all pelvic floor repairs. Nonetheless, the Prolift+M IFU warns surgeons on 3 separate occasions that this knowledge is a prerequisite to incorporating Prolift +M in surgical practice.

In addition, it is clear from the literature cited above, from my own personal experience, and from common sense, that surgeons with experience in pelvic floor surgery, familiarity with pelvic anatomy, and those trained in proper technique and handling of mesh will have better outcomes after mesh-augmented repairs than that of surgeons without this experience, familiarity or training. Again, Ethicon has certainly done its part in warning users that they should be adequately trained before using the device.

As with the PROLIFT IFU, the PROLIFT+M IFU warns that the surgeon should "avoid placing excessive tension on the mesh implant during placement." Given the tension-free design of the product, the fact remains that the surgical error of placing the mesh under tension may result in pain. Avoiding this surgical mistake is critical, as is made clear by the PROLIFT+M IFU, the Prolift Surgeon's Monograph and professional education materials.

The Prolift+M IFU also appropriately reflects the potential risks that are reflected in the medical literature. Adverse reactions explicitly stated in the Prlift+M IFU include "those typically associated with all surgery employing implantable materials of this type, including hematoma, urinary incontinence, urinary retention/obstruction, ureter obstruction, voiding dysfunction, pain, infection potentiation, wound dehiscence, nerve damage, recurrent prolapse, inflammation, adhesion formation, fistula formation, contracture, scarring, and mesh exposure, erosion, or extrusion." It goes on to state, "Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time." Further, "Dissection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time."

Finally, the PROLIFT+M IFU also discloses at the top of the first page that "The safety and effectiveness of he GYNECARE PROLIFT+M Systems compared to conventional surgical repair for pelvic organ prolapse have not been demonstrated in randomized controlled clinical trials." Though these trials were underway at the time of the publication of both PROLIFT+M IFUs, they had not been published until after publication as noted in the section above.

The Impact of Surgeon Experience and Volume on Outcomes with Transvaginal Mesh Surgery

As noted above, there is a wide variation in outcomes with respect to mesh-related complications, as well as traditional repairs. This suggests that surgeon experience, volume and/or technique may play a role. The Prolift and Prolift+M IFUs repeatedly reference surgical technique and experience as important in surgical success. Authors

cited in this report with regard to Prolift and Prolift +M attribute some of their outcomes to their learning curve, whereby as surgical volume increases, outcomes improve.[152] [153] Blandon et al. also correlated surgical expertise and subspecialty training with complications from transvaginal mesh surgery.[154] Withagen et al. attributed their high erosion rate of 17% to surgical experience.[155] Higher surgeon volume has been shown in many studies to be correlated with more successful outcomes in several different surgical specialties, including urology, gynecology, general surgery, and orthopedics.[156][157][158][159][160]

Eilber et al. looked at surgeon volume and specialty with respect to outcomes after vaginal prolapse surgery with mesh.[161] Using de-identified file data on Medicare beneficiaries, the authors identified 1657 surgeries for prolapse using mesh between 2007 and 2008 (prior to FDA PHN and subsequent litigation) utilizing procedure code 57267. Additional procedure codes were used to identify which of these subjects underwent re-operation. Surgeons were classified as low-, intermediate-, or high-volume based on the number of prolapse procedures with mesh performed during the study period. The authors found that 53% of surgeons performed only 1 procedure annually, 25%

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[152] Ubertazzi EP et al: Long-term outcomes of transvaginal mesh (TVM) in patients with pelvic organ prolapse: A 5-year follow-up. Euro J Ob Gyn Reprod Bio, 2018.
[153] Lensen EJM, et al: Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study. Int Urogynecol J 2013
[154] Blandon et al: Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J, 2009
[155] Withagen MI et al: Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. ObGyn, 2011
[156] Rogo-Gupta LJ et al: The effect of surgeon volume on outcomes and resource for vaginal hysterectomy. Obstet Gynecol, 2010
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[158] Trinh QD et al: A systematic review of the colume-outcome relationship for radical prostatectomy. Eur Urol, 2013
[159] Zevin B et al: Volume-outcome association in bariatric surgery: a systematic review. Ann Surg, 2012
[160] Critchley RJ et al: Does surgical volume affect outcome after primary revision and knee arthoplasty? A systematic review of the literature. Knee 2012
[161] Eilber KS et al: The role of the surgeon on outcomes of vaginal prolapse surgery with mesh. Female Pelvic Med & Recon Surg, 2017.

performed 2 procedures annually, and 22% performed 3 or more mesh prolapse repairs annually. Based on quartiles, low-volume surgeons were defined as those performing 1 case per year, intermediate-volume surgeons as those performing 2 cases annually, and high-volume surgeons as those performing 3 or more cases per year. Thus, the majority of physicians performing mesh prolapse repair (78%) were surgeons who performed 2 or fewer of these surgeries per year. Further, of the 368 procedures performed by high-volume surgeons, 46% were performed by surgeons doing 3 cases per year, and 54% were done by surgeons who performed 4 to 8 per year, while only 4% were done by surgeons performing at least 8 cases annually. The cumulative reoperation rate for low-volume surgeons (6%) was significantly higher than that of intermediate- and high-volume surgeons (2%, 3%). The cumulative re-operation rates for gynecologists and urologists were equivalent at 4%. This data supports the concept that "increased surgeon experience has an influential role in outcomes of vaginal surgery with mesh." The authors further concluded, "The findings of our study suggest that surgeon inexperience may have contributed to a significant proportion of mesh-related complications, prompting the first FDA safety communication in 2008." They further go on to state that since 78% of vaginal prolapse surgery with mesh was performed by low- and intermediate-volume surgeons, "it is possible that the number of negative mesh-related outcomes subsequent to the study period may have been reduced if more of the cases had been performed by high-volume surgeons."

SUMMARY OF OPINIONS:

For the reasons set forth above, the following are my opinions to a reasonable degree of medical certainty. I reserve the right to update my opinions based upon my review of additional information or data.

In forming my opinions, I relied most heavily on the published medical literature and my surgical experience and training, than on other sources such as internal company documents or company witness deposition testimony. Though I have reviewed hundreds of company documents related to Prolift and Prolift+M and have reviewed the deposition transcripts of company witnesses, this type of evidence does not hold as much value in forming my opinions as the scientific evidence that is available in the form of a large volume of peer reviewed published medical literature. As a medical and surgical expert, it is my responsibility to rely upon science over the words of a company employee and the medical data over pontification and speculation to formulate my opinions. Moreover, I formed my opinions based on the overall body of relevant published literature, rather than on individual studies.

1. Gynecare Prolift and Prolift +M were safe and effective products that were supported by a substantial body of clinical data which supported its use as a means of achieving superior objective and subjective efficacy outcomes relative to native tissue and biologic repairs, with adverse event rates within the range expected for all prolapse repairs. They were suitable options for many women who suffered from bothersome pelvic organ prolapse who may have been at risk for recurrence from, or who may have failed, prior native tissue repairs. It was also a suitable alternative to the more invasive and morbid sacral colpopexy, whether done in an open or robotic/laparoscopic manner.

Based on my experience with over 500 surgical procedures to treat pelvic organ prolapse, it is my opinion that Prolift and Prolift +M were not defectively designed. In fact, to this day I treat patients whom I believe would benefit from the products if they were still available. By bringing Prolift and Prolift +M to the market, Ethicon delivered women a viable transvaginal option for a durable and less invasive repair. The risk/benefit ratio of these products appealed to many women who unfortunately no longer have this choice available to them.

2. The meshes used in the Prolift and Prolift +M implants are safe and effective materials for use in the treatment of pelvic organ prolapse. Polypropylene mesh and polypropylene sutures have been in surgical use for decades. As a clinician with extensive experience in implanting mesh for the treatment of stress incontinence and prolapse and managing the post-operative course of patients, it is my opinion that the pore sizes of the meshes used in Prolift and Prolift +M are large enough to allow for the proper tissue ingrowth necessary for physiologic incorporation.

3. A foreign body/inflammatory response is an expected and physiological outcome of the placement of any surgical implant. There is no body of medical literature demonstrating that this response has negative, clinical impact on clinical outcomes when Prolift or Prolift +M are placed correctly.

4. The extensive clinical data on Prolift, Prolift +M and mesh slings also knitted of PROLENE® (TVT, TVT-O) does not demonstrate that the mesh in these products degrades in the human body in any manner that has a clinical impact on women. If it did, surgeons, including myself, would see far lower long-term efficacy in their repairs and this would be likewise reflected in the data.

5. There is a lack of data establishing that chronic pelvic pain and dyspareunia are consistently the result of contraction in the absence of over-tensioning the implant. It is my experience that if Prolift or Prolift +M is placed tension-free as described in the IFU and as can be seen in professional education materials, contraction seldom has clinical implications for the patient. It is clear from a large body of evidence that dyspareunia rates after Prolift and Prolift +M and other mesh repairs are consistent with and in some cases lower than the dyspareunia rates after a variety of native tissue repairs. Further, the complexity and multifactorial nature of dyspareunia in aging women, particularly in the setting of concomitant multicompartment surgery, make it difficult to associate the disorder with the mesh, particularly in long-term studies when aging and/or abstinence alone may be responsible for dyspareunia.

6. The potential risks of Prolift and Prolift +M are appropriately described in their IFU's the Prolift Surgeon's Resource Monograph and in Ethicon's other professional education materials for Prolift, particularly when taking into consideration the base of surgical and anatomic knowledge held by a surgeon who has been trained to use the product. The importance of surgical experience and training are explicitly stated in the products' IFUs.

7. Based on the medical literature discussed above, there is no design of device or implant that reduces or mitigates the potential risks associated with these implants. While non-mesh surgeries do not pose risks that are specific to mesh (mesh exposure), they pose increased risks of failure of treatment, and do not eliminate other risks of vaginal surgery such as dyspareunia or pain, temporary or chronic.

8. The experience of the surgeon, surgeon's volume, and patient selection play an important role in the outcomes of surgery, including the mesh-augmented vaginal repair of prolapse. These factors bely the variations in the medical literature with respect to the outcomes of Prolift and Prolift +M, and may explain why so many women have benefited with no or very minimal complications from Prolift and Prolift+M, while others have developed complications and/or recurrence.

9. Dyspareunia, especially in aging women, is a complicated and multifactorial disorder that often cannot simply be attributed to transvaginal mesh in and of itself. Consideration of other factors must be considered when assessing women with dyspareunia after pelvic floor surgery.

CONCLUSION:

Based on my extensive personal experience and my review of the substantial medical literature, it is my strongly held opinion that Prolift revolutionized the treatment of pelvic organ prolapse and has resulted in high satisfaction in the vast majority of my patients. It offered women a valid, effective and safe alternative to the recurrence-prone native tissue repair or the more morbid transabdominal major operation. Women in the 21st century lead busy and active lives, even as they age. It has been and continues to be my experience that women prefer a transvaginal rather than transabdominal procedure. They want a procedure that is durable yet safe. They need to get back to their work, their children, their grandchildren, their spouses and their busy lives faster and without a prolonged recovery. Prolift fulfilled these needs, and the data supported it. Even now, 10 years after the initial FDA warning on the usage of transvaginal mesh, large meta-

analyses have proven the usage of transvaginal mesh to be a safe and effective alternative to the native tissue repair or sacral colpopexy in properly selected patients.

Dated: July 30, 2018

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